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Publication Title:

4-HETEROCYCLYL-SUBSTITUTED QUINAZOLINE DERIVATIVES,
PROCESSES FOR THEIR PREPARATION AND THEIR USE AS
ANTI-CANCER AGENTS

Abstract:

This invention relates to certain 4-aminoquinazolines of formula (I) and the pharmaceutically acceptable salts and stereoisomers thereof wherein Z is: formula (II), formula (III), formula (IV) or formula (V) wherein X is methylene, thio, -N(H)- or oxy; Y completes a 5 or 6 membered aromatic, or partially saturated ring which may incorporate an oxygen or sulfur atom; T is methylene, -N(H)-, thio or oxy; or Z is formula (VI) wherein D may be saturated carbon, oxy or thio; or Z is formula (VIII) wherein A completes a 7 to 9 membered mono-unsaturated mono-aza ring; R<1>, R<2>, R<3>, m, n, p and q are defined as in the description. The compounds of formula (I) are useful for the treatment of hyperproliferative diseases, particularly as anti-cancer agents.

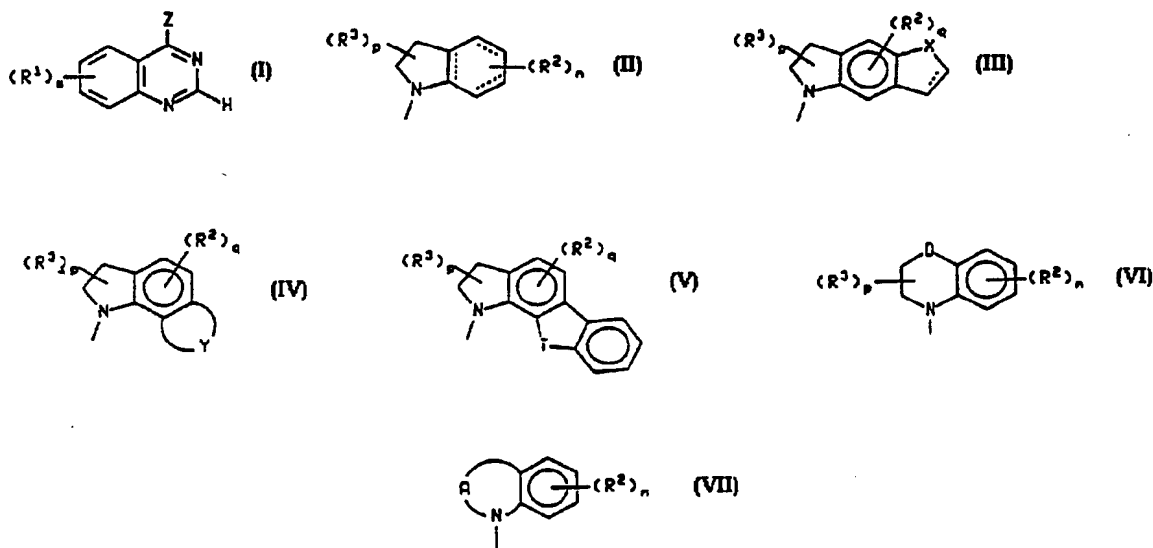
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(54) Title: 4-HETEROCYCLYL-SUBSTITUTED QUINAZOLINE DERIVATIVES, PROCESSES FOR THEIR PREPARATION AND THEIR USE AS ANTI-CANCER AGENTS

**(57) Abstract**

This invention relates to certain 4-aminoquinazolines of formula (I) and the pharmaceutically acceptable salts and stereoisomers thereof wherein Z is: formula (II), formula (III), formula (IV) or formula (V) wherein X is methylene, thio, -N(H)- or oxy; Y completes a 5 or 6 membered aromatic, or partially saturated ring which may incorporate an oxygen or sulfur atom; T is methylene, -N(H)-, thio or oxy; or Z is formula (VI) wherein D may be saturated carbon, oxy or thio; or Z is formula (VII) wherein A completes a 7 to 9 membered mono-unsaturated mono-aza ring; R¹, R², R³, m, n, p and q are defined as in the description. The compounds of formula (I) are useful for the treatment of hyperproliferative diseases, particularly as anti-cancer agents.

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4-HETEROCYCLYL-SUBSTITUTED QUINAZOLINE DERIVATIVES, PROCESSES FOR THEIR PREPARATION AND THEIR USE AS ANTI-CANCER AGENTS.

Background of the Invention

This invention relates to quinazoline derivatives and methods of using the same, particularly as anti-cancer agents, in mammals.

5 Many of the current treatment regimes for cancer utilize compounds which inhibit DNA synthesis. Such compounds are toxic to cells generally but their toxic effect on the rapidly dividing tumor cells can be beneficial. Alternative approaches to anti-cancer agents which act by mechanisms other than the direct inhibition of DNA synthesis have been explored in order to enhance the selectivity of action against
10 cancer cells.

It is known that a cell may become cancerous by virtue of the transformation of a portion of its DNA into an oncogene (i.e. a gene which, on activation, leads to the formation of malignant tumor cells). Many oncogenes encode proteins which are aberrant tyrosine kinases capable of causing cell transformation. Alternatively, the
15 overexpression of a normal proto-oncogenic tyrosine kinase may also result in proliferative disorders, sometimes resulting in a malignant phenotype.

Receptor tyrosine kinases are large enzymes which span the cell membrane and possess an extracellular binding domain for growth factors such as epidermal growth factor, a transmembrane domain, and an intracellular portion which functions as a
20 kinase to phosphorylate specific tyrosine residues in proteins and hence to influence cell proliferation. It is known that such kinases are frequently aberrantly expressed in common human cancers such as breast cancer, gastrointestinal cancer such as colon, rectal or stomach cancer, leukemia, and ovarian, bronchial or pancreatic cancer. It has also been shown that epidermal growth factor receptor (EGFR) which possesses
25 tyrosine kinase activity is mutated and/or overexpressed in many human cancers such as brain, lung, squamous cell, bladder, gastric, breast, head and neck, oesophageal, gynecological and thyroid tumors.

Accordingly, it has been recognized that inhibitors of receptor tyrosine kinases are useful as a selective inhibitors of the growth of mammalian cancer cells. For
30 example, erbstatin, a tyrosine kinase inhibitor selectively attenuates the growth in athymic nude mice of a transplanted human mammary carcinoma which expresses

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epidermal growth factor receptor tyrosine kinase (EGFR) but is without effect on the growth of another carcinoma which does not express the EGF receptor.

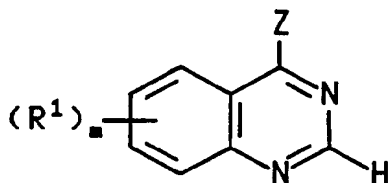
Various other compounds, such as styrene derivatives, have also been shown to possess tyrosine kinase inhibitory properties. More recently three European patent publications, namely EP 0 566 226 A1, EP 0 602 851 A1 and EP 0 520 722 A1 have disclosed that certain quinazoline derivatives possess anti-cancer properties which result from their tyrosine kinase inhibitory properties. Also PCT publication WO 92/20642 discloses bis-mono and bicyclic aryl and heteroaryl compounds as tyrosine kinase inhibitors.

In addition U.S. Patent No. 4,012,513 discloses certain 1-(heterocyclic)-indol-3-yl-acetic acid derivatives that have anti-inflammatory, analgesic and antipyretic activity.

Although the anti-cancer compounds described above make a significant contribution to the art there is a continuing search in this field of art for improved anti-cancer pharmaceuticals.

Summary of the Invention

This invention is directed to quinazoline derivatives, particularly 4-amino-quinazolines, that are useful as anti-cancer agents. The compounds of this invention have the Formula I

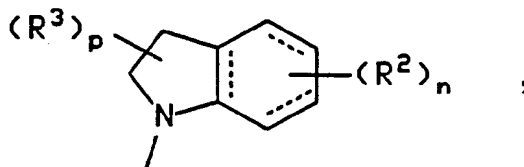


Formula I

and the pharmaceutically acceptable salts and stereoisomers thereof wherein either A, B or C

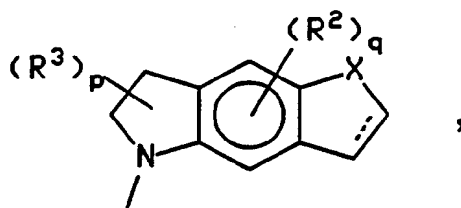
A:

Z is



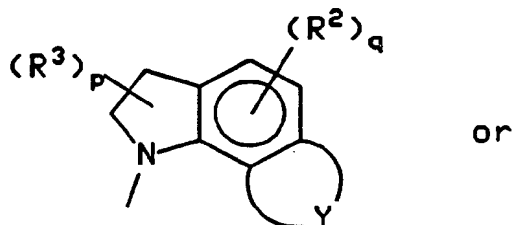
Formula II

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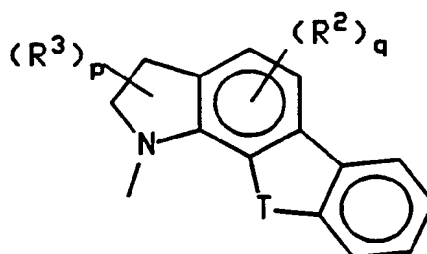
Formula III



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or

Formula IV



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Formula V

wherein

X is methylene, thio, -N(H)- or oxy;

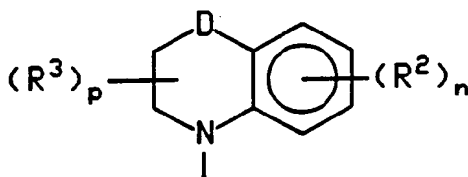
Y completes a 5 or 6 membered aromatic, or partially saturated ring which may
 25 incorporate an oxygen or sulfur atom;

T is methylene, -N(H)-, thio or oxy;

B:

Z is

-4-



5

Formula VI

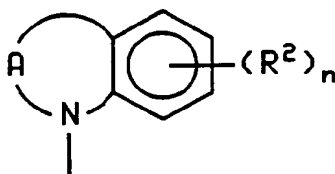
wherein D may be saturated carbon, oxy or thio;

or

C:

10

Z is



15

Formula VIII

wherein A completes a 7 to 9 membered mono-unsaturated mono-aza ring;

R¹ for each occurrence is independently

- a. trifluoromethyl, halo, nitro, hydroxy, amino, cyano, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₁-C₄)alkoxycarbonyl, (C₁-C₄)alkanoyloxy, (C₁-C₄)alkanoylamino, carboxy, phenoxy, benzoyloxy, carbamoyl, mono-N or di-N,N-di-(C₁-C₄)alkylcarbamoyl, mono-N or di-N,N-(C₁-C₄)alkylamino, mono-N or di-N,N-(hydroxy(C₂-C₄)alkyl)amino, mono-N or di-N,N-((C₁-C₄)alkoxy(C₂-C₄)alkyl)amino, anilino, pyrrolidin-1-yl, piperidin-1-yl, morpholino, piperazin-1-yl, 4-(C₁-C₄)alkylpiperazin-1-yl, (C₁-C₄)alkylthio, phenylthio, or such groups substituted on (C₁-C₄)alkyl;

25

- b. hydroxy(C₂-C₄)alkoxy(C₁-C₄)alkyl, (C₁-C₄)alkoxy-(C₂-C₄)alkoxy-(C₁-C₄)alkyl, hydroxy(C₂-C₄)alkylthio(C₁-C₄)alkyl, (C₁-C₄)alkoxy(C₂-C₄)alkylthio(C₁-C₄)alkyl, hydroxyamino, benzoylamino, mono-N or di-N,N-(C₁-C₄)alkylcarbamoylmethylamino, carbamoylmethylamino, (C₁-C₄)alkoxycarbonylamino, (C₁-C₄)alkanoylamino, carboxymethylamino, (C₁-C₄)alkoxycarbonylmethylamino, (C₁-C₄)alkoxyamino, (C₂-C₄)alkanoyloxyamino, phenyl(C₁-C₄)alkylamino, (C₁-C₄)alkylsulphonylamino, benzenesulphonamido, 3-phenylureido, 2-oxopyrrolidin-1-yl, 2,5-dioxopyrrolidin-1-yl, ureido, (C₁-C₄)alkoxy(C₁-C₄)alkylcarbonylamino, (C₁-C₄)alkylsulfinyl,

30

(C₁-C₄)alkylsulfonyl, (C₁-C₄)alkoxy(C₂-C₄)alkylthio, mono-, di- or trifluoromethoxy, (C₁-C₄)alkylenedioxy, benzyloxy, azido, guanidino, aminocarbonyl, mono-N- or di-N,N-(C₁-C₄)alkylaminocarbonyl, phenyl(C₁-C₄)alkoxy, carboxymethoxy, (C₁-C₄)alkoxycarbonylmethoxy, carbamoylmethoxy, mono-N or di-N,N-(C₁-C₄)alkyl
 5 carbamoylmethoxy, mono-N- or di-N,N-(hydroxy(C₂-C₄)alkyl)carboxamido, mono-N- or di-N,N-((C₁-C₄)alkoxy (C₂-C₄)alkyl)carboxamido or bis((C₁-C₄)alkanesulfonyl)amido; or
 c. (C₂-C₄)alkoxy, (C₂-C₄)alkylthio, (C₂-C₄)alkanoyloxy, (C₂-C₄)alkylamino, (C₁-C₄)alkyl(C₁-C₄)alkylenedioxy, or (C₂-C₄)alkanoylamino; each such group substituted with
 amino, halo, hydroxy, (C₂-C₄)alkanoyloxy, (C₁-C₄)alkoxy, mono-N- or di-N,N-(C₁-
 10 C₄)alkylamino, mono-N or di-N,N-(hydroxy(C₂-C₄)alkyl)amino, mono-N or di-N,N-((C₁-C₄)alkoxy(C₂-C₄)alkyl)amino, (C₁-C₄)alkanoylamino, phenoxy, anilino, imidazol-1-yl, phenylthio, piperidino, morpholino, piperazin-1-yl-, 4-(C₁-C₄)alkylpiperazin-1-yl-, carboxy, (C₁-C₄)alkoxycarbonyl, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, carboxamido, mono-N- or di-N,N-(C₁-C₄)alkylcarboxamido or mono-N- or di-N,N-
 15 (hydroxy(C₂-C₄)alkyl)carboxamido;

wherein any phenyl in a R¹ substituent is optionally mono- or di- substituted with halo, nitro, trifluoromethyl, hydroxy, (C₁-C₄)alkoxy or (C₁-C₄)alkyl and said (C₁-C₄)alkylenedioxy is linked at both ends to the quinazoline moiety;

R² for each occurrence is independently mono-, di- or tri-fluoromethyl, halo,
 20 nitro, hydroxy, amino, azido, isothiocyano, (C₁-C₄)alkyl, phenyl, thienyl, (C₁-C₄)alkoxy, benzyloxy, phenoxy, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₁-C₄)alkylenedioxy, cyano, benzoylamino, trifluoromethylcarbonylamino, (C₁-C₄)alkanoylamino, (C₁-C₄)alkanoyl, N-mono- or N,N-di-(C₁-C₄)alkylamino, (C₁-C₄)alkylsulfonylamino, trifluoromethylsulfonylamino, (C₁-C₄)alkylthio, (C₁-C₄)alkylsulfinyl or (C₁-C₄)alkylsulfonyl,
 25 pyrrol-1-yl, piperidin-1-yl or pyrrolidin-1-yl, said phenyl, benzyloxy, phenoxy and benzoylamino optionally mono-substituted with halo, nitro, trifluoromethyl, hydroxy or (C₁-C₄)alkyl and said (C₁-C₄)alkylenedioxy is linked at both ends to adjacent carbons on the benzene moiety;

R³ for each occurrence is independently hydroxy, amino, N-mono- or N,N-di-(C₁-
 30 C₄)alkylamino, sulfo, or (C₁-C₄)alkoxy (provided that such groups are not attached to a ring carbon which is adjacent to an oxy, thio or -N-), or R³ for each occurrence is independently carboxy, hydroxy(C₁-C₄)alkyl, (C₁-C₄)alkoxy(C₁-C₄)alkyl, amino(C₁-C₄)alkyl, mono-N- or di-N,N-(C₁-C₄)alkylamino(C₁-C₄)alkyl, morpholino (C₁-C₄)alkyl, 4-

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(C₁-C₄)alkyl-piperazin-1-yl(C₁-C₄)alkyl, carboxy(C₁-C₄)alkyl, (C₁-C₄)alkoxycarbonyl, sulfo(C₁-C₄)alkyl or (C₁-C₄)alkyl;

where m is 0-3;

n is 0-4;

5 p is 0, 1 or 2; and

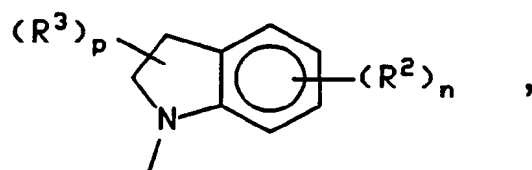
q is 0, 1 or 2;

with the proviso that 4-(3,4-dihydro-2H-quinolin-1-yl)-quinazoline is not included.

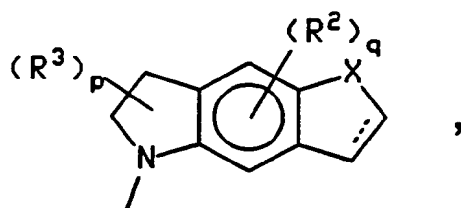
A first group of preferred compounds of Formula I consists of those compounds

wherein

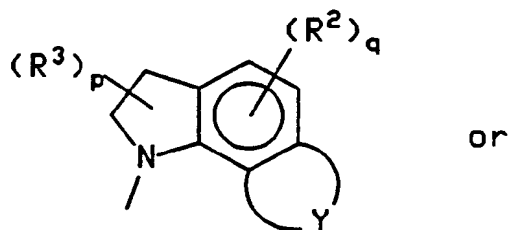
10 Z is



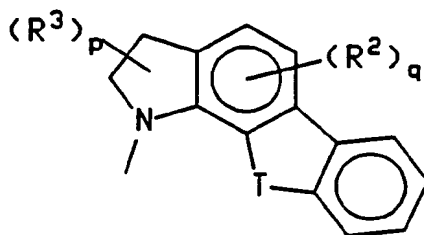
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-7-

R¹ for each occurrence is independently hydroxy, (C₁-C₄)alkoxy, hydroxy(C₂-C₄)alkoxy, amino(C₂-C₄)alkyl, amino(C₂-C₄)alkoxy, (C₁-C₄)alkoxy(C₂-C₄)alkoxy, (C₁-C₄)alkylenedioxy, hydroxy(C₁-C₄)alkyl(C₁-C₄)alkylenedioxy, (C₁-C₄)alkoxy(C₁-C₄)alkyl(C₁-C₄)alkylenedioxy, mono-N- or di-N,N-(C₁-C₄)alkylamino(C₂-C₄)alkoxy, 3- or
 5 4-(C₁-C₄)alkoxy-(2-hydroxy)-(C₃-C₄)alkoxy, carboxy(C₁-C₄)alkoxy, morpholino(C₂-C₄)alkoxy, imidazol-1-yl(C₂-C₄)alkoxy, 4(C₁-C₄)alkylpiperazin-1-yl-(C₂-C₄)alkoxy, (C₁-C₄)alkoxy(C₁-C₄)alkanoyloxy, nitro, hydroxylamino, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, (C₁-C₄)alkanoylamino, hydroxy(C₂-C₄)alkylamino, (C₁-C₄)alkoxy(C₂-C₄)alkylamino, (C₁-C₄)alkylsulfonamido, morpholino, (C₁-C₄)alkyl-piperazin-1-yl, bis(C₁-
 10 C₄)alkanesulfonamido, di(C₁-C₄)alkylamino(C₂-C₄)alkylamino, (C₁-C₄)alkylamino(C₂-C₄)alkylamino, imidazol-1-yl, piperidin-1-yl, pyrrolidin-1-yl, (C₁-C₄)alkoxy(C₁-C₄)alkylcarbonylamino, N-(C₁-C₄)alkyl-N-(C₁-C₄)alkanoyl-amino, carboxy, (C₁-C₄)alkoxycarbonyl, (C₁-C₄)alkoxycarbonyl(C₁-C₄)alkoxy, amido, mono-N- or di-N,N-(C₁-C₄)alkylaminocarbonyl, mono-N- or di-N,N-(hydroxy(C₂-C₄)alkyl)aminocarbonyl, (C₁-
 15 C₄)alkyl, hydroxy(C₁-C₄)alkyl, mono-N- or di-N,N-((C₁-C₄)alkoxy(C₁-C₄)alkyl)amino(C₁-C₄)alkyl, mono-N- or di-N,N-(C₁-C₄)alkylamino(C₁-C₄)alkyl, (C₁-C₄)alkanoylamino(C₁-C₄)alkyl, (C₁-C₄)alkoxy(C₂-C₄)alkoxy(C₁-C₄)alkyl, (C₁-C₄)alkylthio, (C₁-C₄)alkoxy(C₂-C₄)alkylthio or hydroxy(C₂-C₄)alkylthio;

R² for each occurrence is independently nitro, halo, (C₁-C₄)alkyl, pyrrol-1-yl, hydroxyl, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, amino(C₁-C₄)alkyl, azido, ethenyl, ethynyl, (C₁-C₄)alkylenedioxy, phenyl or (C₁-C₄)alkylthio;

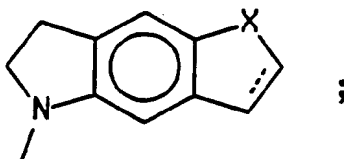
R³ for each occurrence is independently hydroxy(C₁-C₄)alkyl, (C₁-C₄)alkyl, amino(C₁-C₄)alkyl, carboxy(C₁-C₄)alkyl or mono-N- or di-N,N-(C₁-C₄)alkylamino(C₁-C₄)alkyl;

25 m is 0, 1 or 2;
 p is 0 or 1; and
 n is 0, 1, 2, or 3.

Within this first group of preferred compounds of Formula I are a first group of especially preferred compounds wherein

30 Z is

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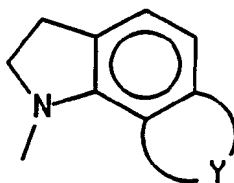
5 X is -N(H)-; and

R¹ for each occurrence is substituted independently in the 6 and/or 7 position.

A second group of especially preferred compounds within the above first group of preferred compounds of Formula I are compounds wherein

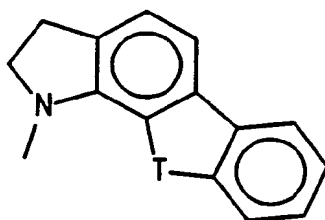
Z is

10



15

or



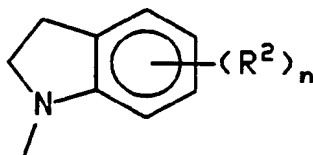
20

; and

R¹ for each occurrence is substituted in the 6 and/or 7 position.

25 A third group of especially preferred compounds within the above first group of preferred compounds of Formula I are compounds wherein

Z is



30

n is 1, 2 or 3;

m is 1 or 2;

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R^1 for each occurrence is substituted independently in the 6 and/or 7 positions and is (C_1-C_4) alkyl, (C_1-C_4) alkoxy, hydroxy (C_2-C_4) alkoxy, (C_1-C_4) alkoxy (C_2-C_4) alkoxy, carboxy (C_1-C_4) alkoxy, (C_1-C_4) alkoxycarbonyl (C_1-C_4) alkoxy, imidazol-1-yl (C_2-C_4) alkoxy, morpholino (C_2-C_4) alkoxy, 4- (C_1-C_4) alkylpiperazin-1-yl (C_1-C_4) alkoxy, (C_1-C_4) alkoxy-2-hydroxy (C_3-C_4) alkoxy, amino, (C_1-C_4) alkylamino, di-N,N-alkylamino, (C_1-C_4) alkanoylamino, (C_1-C_4) alkylsulfonylamido, morpholino, (C_1-C_4) alkylpiperazin-1-yl, mono-N- or di-N,N- (C_1-C_4) alkylamino (C_2-C_4) alkylamino; and

R^2 for each occurrence is independently 4-hydroxy, 4-amino, 5-fluoro, 5-hydroxy, 5-amino, 6-halo, 6-methyl, 6-ethenyl, 6-ethynyl, 6-nitro or 7-methyl.

10 Particularly preferred compounds within the above group of especially preferred compounds are compounds wherein

R^2 for each occurrence is independently halo, nitro, hydroxy or methyl;

R^1 is (C_1-C_4) alkoxy or (C_1-C_4) alkyl;

m is 2; and

15 n is 1 or 2.

Other particularly preferred compounds within the above group of especially preferred compounds are compounds wherein

a. m is 2;

R^1 is 6-methoxy;

20 R^1 is 7-methoxy;

n is 2 ;

R^2 is 5-fluoro; and

R^2 is 6-bromo;

b. m is 2;

25 R^1 is 6-(2-methoxyethoxy);

R^1 is 7-(2-methoxyethoxy) ;

n is 1 ; and

R^2 is 6-chloro;

c. m is 2;

30 R^1 is 6-methoxy;

R^1 is 7-(2-hydroxyethoxy);

n is 1 ; and

R^2 is 6-chloro;

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- d. m is 1;
R¹ is 6-amino;
n is 1; and
R² is 6-chloro;
- 5 e. m is 2;
R¹ is 6-methoxy;
R¹ is 7-(3-hydroxypropoxy);
n is 1; and
R² is 6-chloro;
- 10 f. m is 2;
R¹ is 7-(2-imidazol-1-yl-ethoxy);
R¹ is 6-methoxy;
n is 1; and
R² is 6-chloro;
- 15 g. m is 2;
R¹ is 6-methoxy;
R¹ is 7-methoxy;
n is 1; and
R² is 5-amino;
- 20 h. m is 2;
R¹ is 6-methoxy;
R¹ is 7-(2-methoxy-ethoxy);
n is 2 ;
R² is 5-fluoro; and
- 25 R² is 6-bromo;
- i. m is 2;
R¹ is 6-methoxy;
R¹ is 7-methoxy;
n is 2;
- 30 R² is 5-amino; and
R² is 6-chloro;

or

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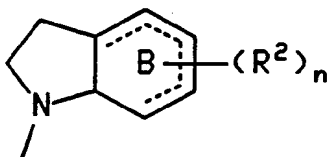
- j. m is 2;
 R¹ is 6-methoxy;
 R¹ is 7-(2-hydroxy-3-methoxy)propoxy;
 n is 1; and
 R² is 6-chloro.

5

A second group of preferred compounds of Formula I are those compounds wherein

Z is

10



the B six membered ring has 0, 1 or 2 double bonds in the dotted line region;
 n is 0-2;

15

R² for each occurrence is independently halo, hydroxy or (C₁-C₄)alkyl;
 m is 0, 1 or 2; and

R¹ for each occurrence is substituted independently in the 6 and/or 7 positions and is hydroxy, (C₁-C₄)alkoxy, hydroxy(C₂-C₄)alkoxy, amino(C₂-C₄)alkyl, amino(C₂-C₄)alkoxy, (C₁-C₄)alkoxy(C₂-C₄)alkoxy, (C₁-C₄)alkylenedioxy, hydroxy(C₁-C₄)alkyl(C₁-C₄)alkylenedioxy, (C₁-C₄)alkoxy(C₁-C₄)alkyl(C₁-C₄)alkylenedioxy, mono-N- or di-N,N-(C₁-C₄)alkylamino(C₂-C₄)alkoxy, 3- or 4-(C₁-C₄)alkoxy-(2-hydroxy)-(C₃-C₄)alkoxy, carboxy(C₁-C₄)alkoxy, morpholino(C₂-C₄)alkoxy, imidazol-1-yl(C₂-C₄)alkoxy, 4(C₁-C₄)alkylpiperazin-1-yl-(C₂-C₄)alkoxy, (C₁-C₄)alkoxy(C₁-C₄)alkanoyloxy, nitro, hydroxylamino, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, (C₁-C₄)alkanoylamino, hydroxy(C₂-C₄)alkylamino, (C₁-C₄)alkoxy(C₂-C₄)alkylamino, (C₁-C₄)alkylsulfonamido, morpholino, (C₁-C₄)alkyl-piperazin-1-yl, bis(C₁-C₄)alkanesulfonamido, di-N,N-(C₁-C₄)alkylamino(C₂-C₄)alkylamino, (C₁-C₄)alkylamino(C₂-C₄)alkylamino, piperidin-1-yl, imidazol-1-yl, pyrrolidin-1-yl, (C₁-C₄)alkoxy(C₁-C₄)alkylcarbonylamino, N-(C₁-C₄)alkyl-N-(C₁-C₄)alkanoyl-amino, carboxy, (C₁-C₄)alkoxycarbonyl, (C₁-C₄)alkoxycarbonyl(C₁-C₄)alkoxy, amido, mono-N- or di-N,N-(C₁-C₄)alkylaminocarbonyl, mono-N- or di-N,N-(hydroxy(C₂-C₄)alkyl)aminocarbonyl, (C₁-C₄)alkyl, hydroxy(C₁-C₄)alkyl, mono-N- or di-N,N-((C₁-C₄)alkoxy(C₁-C₄)alkyl)amino(C₁-C₄)alkyl, mono-N- or di-N,N-(C₁-C₄)alkylamino(C₁-C₄)alkyl,

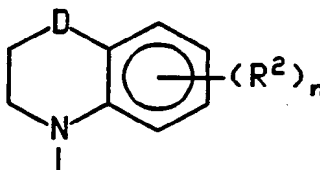
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(C₁-C₄)alkanoylamino(C₁-C₄)alkyl, (C₁-C₄)alkoxy(C₂-C₄)alkoxy(C₁-C₄)alkyl, (C₁-C₄)alkylthio, (C₁-C₄)alkoxy(C₂-C₄)alkylthio or hydroxy(C₂-C₄)alkylthio.

A third group of preferred compounds of Formula I are those compounds wherein

5 Z is



10

D is saturated carbon;

n is 0, 1 or 2;

R² for each occurrence is independently halo, hydroxy, amino, nitro, trifluoromethyl, ethenyl, ethynyl or (C₁-C₄)alkyl;

15 m is 0, 1 or 2; and

R¹ for each occurrence is substituted independently in the 6 and/or 7 positions and is hydroxy, (C₁-C₄)alkoxy, hydroxy(C₂-C₄)alkoxy, amino(C₂-C₄)alkyl, amino(C₂-C₄)alkoxy, (C₁-C₄)alkoxy(C₂-C₄)alkoxy, (C₁-C₄)alkylenedioxy, hydroxy(C₁-C₄)alkyl(C₁-C₄)alkylenedioxy, (C₁-C₄)alkoxy(C₁-C₄)alkyl(C₁-C₄)alkylenedioxy, mono-N- or di-N,N-(C₁-C₄)alkylamino(C₂-C₄)alkoxy, 3- or 4- (C₁-C₄)alkoxy-(2-hydroxy)-(C₃-C₄)alkoxy, carboxy(C₁-C₄)alkoxy, morpholino(C₂-C₄)alkoxy, imidazol-1-yl(C₂-C₄)alkoxy, 4-(C₁-C₄)alkylpiperazin-1-yl-(C₂-C₄)alkoxy, (C₁-C₄)alkoxy(C₁-C₄)alkanoyloxy, nitro, hydroxylamino, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, (C₁-C₄)alkanoylamino, hydroxy(C₂-C₄)alkylamino, (C₁-C₄)alkoxy(C₂-C₄)alkylamino, (C₁-C₄)alkylsulfonamido, morpholino, (C₁-C₄)alkyl-piperazin-1-yl, bis(C₁-C₄)alkanesulfonamido, di-N,N-(C₁-C₄)alkylamino(C₂-C₄)alkylamino, (C₁-C₄)alkylamino(C₂-C₄)alkylamino, imidazol-1-yl, piperidin-1-yl, pyrrolidin-1-yl, (C₁-C₄)alkoxy(C₁-C₄)alkylcarbonylamino, N-(C₁-C₄)alkyl-N-(C₁-C₄)alkanoyl-amino, carboxy, (C₁-C₄)alkoxycarbonyl, (C₁-C₄)alkoxycarbonyl (C₁-C₄)alkoxy, amido, mono-N- or di-N,N-(C₁-C₄)alkylaminocarbonyl, mono-N- or di-N,N-(hydroxy(C₂-C₄)alkyl)aminocarbonyl, (C₁-C₄)alkyl, hydroxy(C₁-C₄)alkyl, mono-N- or di-N,N-((C₁-C₄)alkoxy(C₁-C₄)alkyl)amino(C₁-C₄)alkyl, mono-N- or di-N,N-(C₁-C₄)alkylamino(C₁-C₄)alkyl, (C₁-C₄)alkanoylamino(C₁-C₄)alkyl, (C₁-C₄)alkoxy(C₂-

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C₄)alkoxy(C₁-C₄)alkyl, (C₁-C₄)alkylthio, (C₁-C₄)alkoxy(C₂-C₄)alkylthio or hydroxy(C₂-C₄)alkylthio.

Within this third group of preferred compounds of Formula I are those compounds wherein

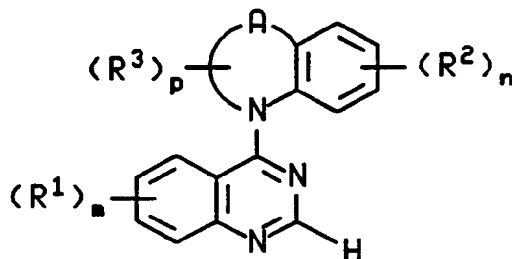
5 R² for each occurrence is independently halo, nitro, hydroxy, (C₁-C₄)alkyl or trifluoromethyl;

R¹ is (C₁-C₄)alkoxy, (C₁-C₄)alkylenedioxy or (C₁-C₄)alkyl;

m is 2; and

n is 1 or 2.

10 Yet another aspect of this invention is a group of preferred compounds within the Formula I compounds, such compounds having the Formula IZ



15

Formula IZ

20 and the pharmaceutically acceptable salts and hydrates thereof wherein

A completes a fused 5 to 9 membered mono-unsaturated, mono-aza ring, wherein said ring having 6 or more members may include an -O- or -S-;

each R¹ taken independently is hydrogen, trifluoromethyl, halo, nitro, hydroxy, amino, (C₁-C₄)alkyl, carboxy, (C₁-C₄)alkoxy, (C₁-C₄)alkoxy(C₁-C₄)alkylene, (C₁-C₄)alkoxy(C₂-C₄)alkoxy, hydroxy(C₂-C₄)alkoxy, trifluoromethyloxy, (C₁-C₄)alkoxycarbonyl, (C₁-C₄)alkylenedioxy, (C₁-C₄)alkylsulfinyl, (C₁-C₄)alkylsulfonyl, pyrrolidin-1-yl, piperidin-1-yl, morpholino, 4-(C₁-C₄)alkylpiperazin-1-yl, carbamoyl, N,N-di-(C₁-C₄)alkylcarbamoyl, phenoxy, benzyloxy, hydroxyamino, (C₁-C₄)alkoxyamino, N,N-di-(C₁-C₄)alkylamino, (C₁-C₄)alkoxycarbonylamino, (C₁-C₄)alkanoylamino, carbamoylamino or benzoylamino, said phenoxy, benzyloxy and benzoylamino optionally mono-substituted with halo, nitro, trifluoromethyl, hydroxy or (C₁-C₄)alkyl and said (C₁-C₄)alkylenedioxy is linked at both ends to the quinazoline moiety;

30

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each R² taken independently is hydrogen, trifluoromethyl, halo, nitro, hydroxy, amino, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, benzyloxy, phenoxy, (C₁-C₄)alkylenedioxy, cyano, benzoylamino, (C₁-C₄)alkanoyl, N,N-di-(C₁-C₄)alkylamino, (C₁-C₄)alkylthio, (C₁-C₄)alkylsulfinyl or (C₁-C₄)alkylsulfonyl, said benzyloxy, phenoxy and benzoylamino
 5 optionally mono-substituted with halo, nitro, trifluoromethyl, hydroxy or (C₁-C₄)alkyl and said (C₁-C₄)alkylenedioxy is linked at both ends to the benzene moiety;

each R³ taken independently is hydroxy, N,N-di-(C₁-C₄)alkylamino, sulfo, (C₁-C₄)alkoxy, provided that such groups are not attached to a ring carbon which is adjacent to an -O- or -S- and that such groups are not at the 2 position, carboxy,
 10 hydroxy(C₁-C₃)alkylene, (C₁-C₄)alkoxy(C₁-C₃)alkylene, N,N-di-(C₁-C₄)alkylamino(C₁-C₃)alkylene, carboxy(C₁-C₃)alkylene, (C₁-C₄)alkoxycarbonyl or sulfo(C₁-C₃)alkylene;

n is 1 or 2;

p is 0, 1 or 2; and

m is 1, 2 or 3.

15 Other compounds within the scope of this invention include:

(6-Chloro-1-(6,7-methylenedioxy-quinazolin-4-yl)-2,3-dihydro-1H-indol-5-yl)-methyl-amine,

3-(6-Chloro-1-(6,7-bis-(2-hydroxy-ethoxy)-quinazolin-4-yl)-2,3-dihydro-1H-indol-3-yl)-propanol,

20 3-(4-(6-Fluoro-7-methyl-2,3-dihydro-indol-1-yl)-7-(3-hydroxy-propoxy)-quinazolin-6-yloxy)-propan-1-ol,

6-Amino-7-hydroxymethyl-4-(6-vinyl-2,3-dihydro-indol-1-yl)-quinazoline,

4-(6-Ethyl-2,3-dihydro-indol-1-yl)-7-methoxy-6-methyl-quinazoline,

1-(6,7-Dimethoxy-quinazolin-4-yl)-6-chloro-2,3-dihydro-1H-indol-4-ol,

25 (4-(6-Bromo-3-(3-morpholin-4-yl-propyl)-2,3-dihydro-indol-1-yl)-quinazolin-6-yl)-methyl-amine,

(4-(6-Chloro-3-(3-dimethylamino-propyl)-2,3-dihydro-indol-1-yl)-7-methoxy-quinazolin-6-yl)-methanol,

30 3-(1-(6,7-Bis-(2-methoxy-ethoxy)-quinazolin-4-yl)-6-fluoro-7-methyl-2,3-dihydro-1H-indol-3-yl)-propionic acid,

2-(4-(3-(3-Dimethylamino-propyl)-3,5,6,7-tetrahydro-2H-pyrrolo[2,3-f]indol-1-yl)-7-(2-hydroxy-ethoxy)-quinazolin-6-yloxy)-ethanol,

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(2-(6-Chloro-1-(2,2-dimethyl-(1,3)dioxolo[4,5-g]quinazolin-8-yl)-2,3-dihydro-1H-indol-3-yl)-ethyl)-diethyl-amine,

N-(4-(6-Ethynyl-7-methyl-2,3-dihydro-indol-1-yl)-7-methoxy-quinazolin-6-ylmethyl)-acetamide,

5 3-(4-(6-Bromo-7-methyl-2,3-dihydro-indol-1-yl)-6-trifluoromethoxy-quinazolin-7-yloxy)-propan-1-ol,

3-(6-Chloro-1-(6,7-bis-(2-methoxy-ethoxy)-quinazolin-4-yl)-2,3-dihydro-1H-indol-3-yl)-methanol,

6-Chloro-1-(7-(2-dimethylamino-ethoxy)-quinazolin-4-yl)-2,3-dihydro-1H-indol-4-ol
10 and

3-(4-(6-Chloro-4-methylamino-2,3-dihydro-indol-1-yl)-6-(3-hydroxy-propoxy)-quinazolin-7-yloxy)-propan-1-ol.

Yet another aspect of this invention is directed to a method for treating a hyperproliferative disorder in a mammal by administering to a mammal suffering from
15 a hyperproliferative disorder, a hyperproliferative disorder treating amount of a Formula I compound.

This invention is also directed to pharmaceutical compositions for the treatment of a hyperproliferative disorder in mammals which comprise a hyperproliferative disorder treating amount of a compound of the Formula I and a pharmaceutically acceptable
20 carrier.

By halo is meant chloro, bromo, iodo, or fluoro.

By alkyl is meant straight chain or branched saturated hydrocarbon.

By mono-unsaturated is meant that the A ring's only unsaturated bond is the bond shared with the benzene ring.

25 Those carbons whose substituents are not otherwise specified are attached to hydrogen (i.e., so that carbon is neutral and possesses a completed octet).

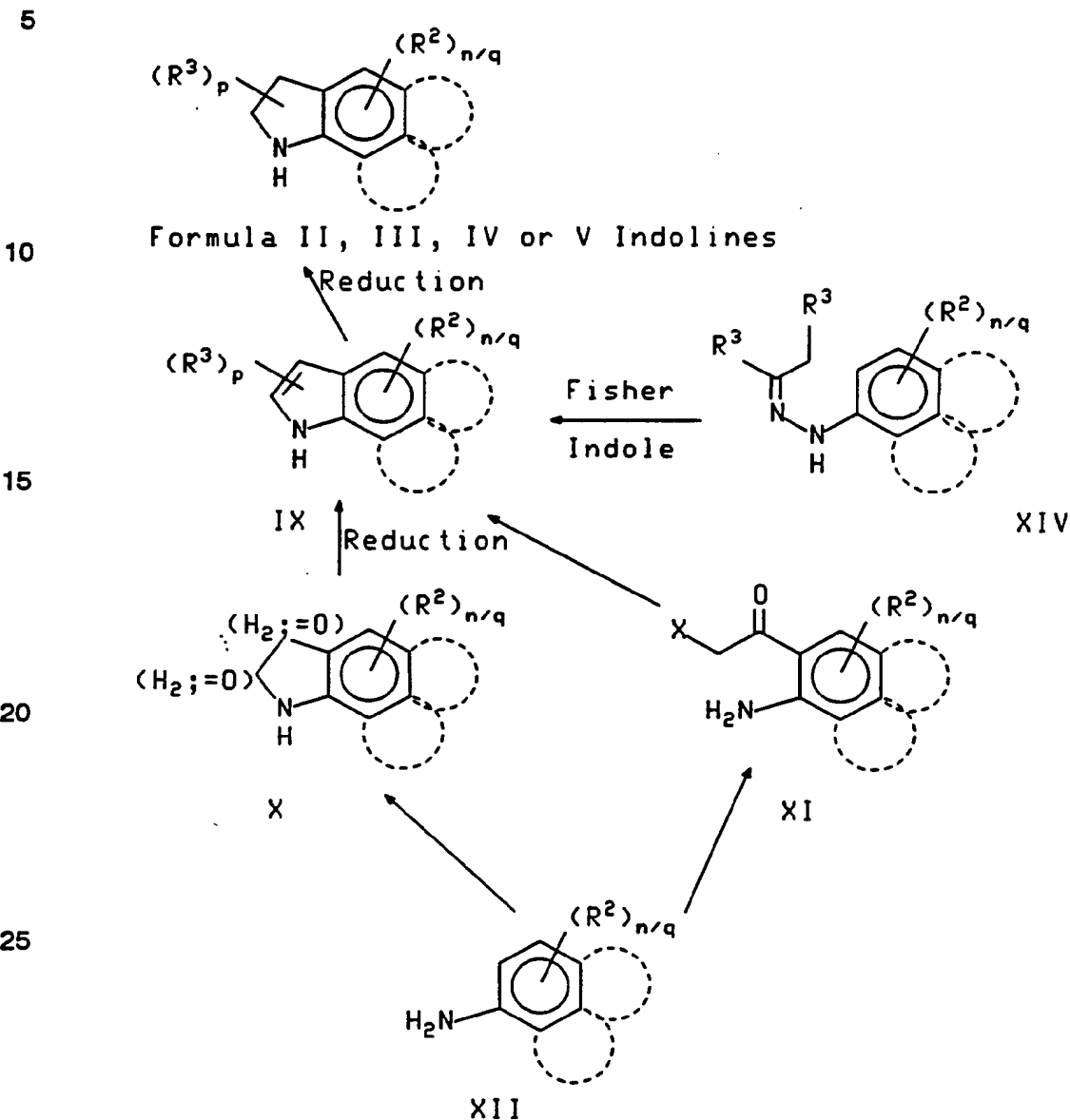
As used herein, the expression "reaction-inert solvent" refers to a solvent which does not interact with starting materials, reagents, intermediates or products in a manner which adversely affects the yield of the desired product.

30 One of ordinary skill will recognize that certain substituents listed in this invention will be chemically incompatible with one another or with heteroatoms in the compounds, and will avoid these incompatibilities in selecting compounds of this invention.

Other features and advantages will be apparent from the specification and claims which describe the invention.

Detailed Description of the Invention

REACTION SCHEME 1



The Formula I compounds, or a pharmaceutically acceptable salt thereof may be prepared by any process known to be applicable to the preparation of chemically-related compounds.

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In general the Formula I quinazolines may be made by preparing the 4-amino adjunct of the appropriately substituted quinazoline using the appropriately substituted amine.

Typically the appropriately substituted 4-haloquinazoline (or a quinazoline bearing a suitable displaceable leaving group in the 4-position such as aryloxy, alkyl sulfonyloxy such as trifluoromethanesulfonyloxy, arylsulfonyloxy, trialkyl-siloxy, cyano, pyrazolo, triazolo or tetrazolo), preferably a 4-chloroquinazoline, is combined with the appropriate amine in a solvent such as a (C₁-C₆)alcohol, dimethylformamide, N-methylpyrrolidin-2-one, chloroform, acetonitrile, tetrahydrofuran (THF), 1,4-dioxane, dimethylsulfoxide or other aprotic solvent. This combination may occur in the presence of a base, and it is preferred that this combination occurs in the presence of an alkali or alkaline earth metal carbonate or hydroxide, or a tertiary amine base, such as pyridine, 2,6-lutidine, collidine, N-methyl-morpholine, triethylamine, diisopropylethylamine, 4-dimethylamino-pyridine or N,N-dimethylaniline. These bases are hereinafter referred to as suitable bases. The mixture is maintained at a temperature of about ambient to about reflux, preferably about 35°C to about reflux, until substantially no remaining 4-haloquinazoline can be detected, typically about 2 hours to about 24 hours. Preferably, the reaction is performed under an inert atmosphere such as dry nitrogen gas.

Generally the reactants are combined stoichiometrically when an amine base is used (alternatively, if an amine base is not used an excess of the amine may be used) however, for those compounds where a salt (typically HCl) of an amine is used, it is preferable to use excess amine base, generally an extra equivalent of amine base.

For those compounds where a sterically hindered amine (such as a 2-alkyl-indoline) or very reactive 4-haloquinazoline is used it is preferable to use t-butyl alcohol or a polar aprotic solvent such as dimethylformamide, dimethylacetamide, or N-methylpyrrolidin-2-one as the solvent.

The following paragraphs facilitate the synthesis of many of the Formula I compounds by appropriate reactions subsequent to the above coupling.

For the production of those compounds of Formula I wherein R¹ is an amino or hydroxyamino the reduction of a Formula I compound wherein R¹ is nitro is employed.

The reduction may conveniently be carried out by any of the many procedures known for such transformations. The reduction may be carried out, for example, by the

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hydrogenation of a solution of the nitro compound in a reaction-inert solvent in the presence of a suitable metal catalyst such as palladium or platinum. Further suitable reducing agents are, for example, sodium dithionite in formic acid or an activated metal such as activated iron (produced by washing iron powder with a dilute solution of an acid such as hydrochloric acid). Thus, for example, the reduction may be carried out by heating a mixture of the nitro compound and the activated metal in a solvent such as a mixture of water and an alcohol, for example, methanol or ethanol, to a temperature in the range, for example, 50 to 150°C, conveniently at or near 70°C.

For the production of those compounds of Formula I wherein R² is an amino, the reduction of a Formula I compound wherein R² is nitro may be used.

For the production of those compounds of Formula I wherein R² or R³ incorporates a primary or secondary amino moiety (other than that amine intended to react with the quinazoline), such free amine is preferably protected prior to the above described reaction followed by deprotection, subsequent to the above described reaction with 4-haloquinazoline.

For a description of protecting groups and their use, see T.W. Greene and P.G.M. Wuts, "Protective Groups in Organic Synthesis", Second Ed., John Wiley & Sons, New York, 1991.

Several well known nitrogen protecting groups can be used. Such groups include (C₁-C₈)alkoxycarbonyl, optionally substituted benzyloxycarbonyl, aryloxycarbonyl, trityl, vinyloxycarbonyl, o-nitrophenylsulfonyl, diphenylphosphinyl, p-toluenesulfonyl, and benzyl. The addition of the nitrogen protecting group may be carried out in a chlorinated hydrocarbon solvent such as methylene chloride or 1,2-dichloroethane, or an ethereal solvent such as glyme, diglyme or THF, in the presence or absence of a tertiary amine base such as triethylamine, diisopropylethylamine or pyridine, preferably triethylamine, at a temperature from about 0°C to about 50°C, preferably about ambient temperature. Alternatively, the protecting groups are conveniently attached using Schotten-Baumann conditions.

Subsequent to the above described amine coupling reaction the protecting group may be removed by deprotecting methods known to those skilled in the art such as trifluoroacetic acid in methylene chloride for the tert-butoxycarbonyl protected products.

For the production of those compounds of the Formula I wherein R¹ is hydroxy, the cleavage of a Formula I compound wherein R¹ is (C₁-C₄)alkoxy is preferred.

The cleavage reaction may conveniently be carried out by any of the many procedures known for such a transformation. Treatment of the quinazoline derivative of Formula I with molten pyridine hydrochloride (20-30 eq.) at 150 to 175°C may be employed for such O-dealkylations. Alternatively, the reaction may be carried out, for example, by treatment of the quinazoline derivative with an alkali metal (C₁-C₄)alkylsulphide such as sodium ethanethiolate or, for example, by treatment with an alkali metal diarylphosphide such as lithium diphenylphosphide. Alternatively the cleavage reaction may conveniently be carried out, for example, by treatment of the quinazoline derivative with a boron or aluminum trihalide such as boron tribromide. Such reactions are preferably carried out in the presence of a reaction-inert solvent and at a suitable temperature.

For the production of those compounds of Formula I wherein R¹ or R² is a (C₁-C₄)alkylsulphinyl or (C₁-C₄)alkylsulphonyl group, the oxidation of a Formula I compound wherein R¹ or R² is a (C₁-C₄)alkylthio group is preferred.

A suitable oxidizing agent is, for example, an agent known in the art for the oxidation of thio to sulphinyl and/or sulphonyl, for example, hydrogen peroxide, a peracid (such as 3-chloroperbenzoic, performic or peracetic acid), an alkali metal peroxysulphate (such as potassium peroxymonosulphate), chromium trioxide or gaseous oxygen in the presence of platinum. The oxidation is generally carried out under as mild conditions as possible and with the required stoichiometric amount of oxidizing agent in order to reduce the risk of over oxidation and damage to other functional groups. In general the reaction is carried out in a suitable solvent such as methylene chloride, chloroform, acetone, tetrahydrofuran or tert-butyl methyl ether and at a temperature, for example, -25 to 50°C, conveniently at or near ambient temperature, that is in the range of 15 to 35°C. When a compound carrying a sulphinyl group is required a milder oxidizing agent may also be used, for example sodium or potassium metaperiodate, conveniently in a polar solvent such as acetic acid or ethanol. It will be appreciated that when a compound of the Formula I containing a (C₁-C₄)alkylsulphonyl group is required, it may be obtained by oxidation of the corresponding (C₁-C₄)alkylsulphinyl compound as well as of the corresponding (C₁-C₄)alkylthio compound.

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For the production of those compounds of Formula I wherein R¹ is (C₂-C₄)alkanoylamino or substituted (C₂-C₄)alkanoylamino, ureido, 3-phenylureido, benzamido, or sulfonamido, the acylation or sulfonylation of a Formula I compound wherein R¹ is amino is appropriate.

5 A suitable acylating agent is, for example, any agent known in the art for the acylation of amino to acylamino, for example an acyl halide (e.g., a (C₂-C₄)alkanoyl chloride or bromide or a benzoyl chloride or bromide), an alkanolic acid anhydride or mixed anhydride (e.g., (C₂-C₄)alkanolic acid anhydride such as acetic anhydride or the mixed anhydride formed by the reaction of an alkanolic acid and a (C₁-C₄)alkoxycarbonyl halide, for example (C₁-C₄)alkoxycarbonyl chloride, in the presence
10 of a suitable base). For the production of those compounds of Formula I wherein R¹ is ureido or 3-phenylureido, a suitable acylating agent is, for example, a cyanate, for example an alkali metal cyanate such as sodium cyanate or, for example, an isocyanate such as phenyl isocyanate. N-Sulfonylations may be carried out with suitable sulfonyl
15 halides or sulfonylanhydrides in the presence of a tertiary amine base. In general the acylation or sulfonylation is carried out in a reaction-inert solvent and at a temperature, in the range, for example, -30 to 120°C, conveniently at or near ambient temperature.

For the production of those compounds of Formula I wherein R¹ is (C₁-C₄)alkoxy or substituted (C₁-C₄)alkoxy or R¹ is (C₁-C₄)alkylamino or substituted mono-N- or di-
20 N,N-(C₁-C₄)alkylamino, the alkylation, preferably in the presence of a suitable base, of a Formula I compound wherein R¹ is hydroxy or amino as appropriate may be preferred.

A suitable alkylating agent is, for example, any agent known in the art for the alkylation of hydroxy to alkoxy or substituted alkoxy, or for the alkylation of amino to
25 alkylamino or substituted alkylamino, for example an alkyl or substituted alkyl halide, for example a (C₁-C₄)alkyl chloride, bromide or iodide or a substituted (C₁-C₄)alkyl chloride, bromide or iodide, in the presence of a suitable base in a reaction-inert solvent and at a temperature in the range, for example, 10 to 140°C, conveniently at or near ambient temperature.

30 For the production of those compounds of Formula I wherein R¹ is an amino-, oxy- or cyano-substituted (C₁-C₄)alkyl substituent, the reaction, preferably in the presence of a suitable base, of a Formula I compound wherein R¹ is a (C₁-C₄)alkyl substituent bearing a displaceable group with an appropriate amine, alcohol or cyanide

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is appropriate. The reaction is preferably carried out in a reaction-inert solvent or diluent and at a temperature in the range, for example, 10 to 100°C, conveniently at or near ambient temperature.

For the production of those compounds of Formula I wherein R¹, R², or R³ is a carboxy substituent or a substituent which includes a carboxy group, the hydrolysis of a Formula I compound wherein the respective R¹, R² or R³ is a (C₁-C₄)alkoxycarbonyl substituent or a substituent which includes a (C₁-C₄)alkoxycarbonyl group is desirable.

The hydrolysis may conveniently be performed, for example, under basic conditions such as an alkali metal hydroxide mediated hydrolysis as illustrated in the accompanying Examples.

For the production of those compounds of Formula I wherein R¹ is amino, (C₁-C₄)alkylamino, di-[(C₁-C₄)alkyl]amino, pyrrolidin-1-yl, piperidino, morpholino, piperazin-1-yl, 4-(C₁-C₄)alkylpiperazin-1-yl or (C₁-C₄)alkythio, the reaction, conveniently in the presence of a suitable base, of a Formula I compound wherein R¹ is a displaceable group with an appropriate amine or thiol may be preferred.

The reaction is preferably carried out, usually in the presence of a suitable base, in a reaction-inert solvent or diluent and at a temperature in the range, for example, 10 to 180°C, conveniently in the range 100 to 150°C.

For the production of those compounds of Formula I wherein R¹ is 2-oxopyrrolidin-1-yl or 2-oxopiperidin-1-yl, the cyclisation, in the presence of a suitable base, of a Formula I compound wherein R¹ is a halogen-(C₂-C₄)alkanoylamino group is convenient.

The reaction is preferably carried out, usually in the presence of a suitable base, in a reaction-inert solvent or diluent and at a temperature in the range, for example, 10 to 100°C, conveniently at or near ambient temperature.

For the production of compounds of Formula I in which R¹ is carbamoyl, substituted carbamoyl, alkanoyloxy or substituted alkanoyloxy, the carbamoylation or acylation of a Formula I compound wherein R¹ is hydroxy is convenient.

Suitable acylating agents are for example any agent known in the art for acylation of hydroxyaryl moieties to alkanoyloxy aryl. For example, (C₂-C₄)alkanoyl halides, (C₂-C₄)alkanoyl anhydrides or mixed anhydrides, and suitable substituted derivatives thereof may be employed, typically in the presence of a suitable base. Alternatively, (C₂-C₄)alkanoic acids or suitably substituted derivatives thereof may be

coupled with a Formula I compound wherein R¹ is hydroxy with the aid of a condensing agent such as a carbodiimide. For the production of those compounds of Formula I in which R¹ is carbamoyl or substituted carbamoyl, suitable carbamoylating agents are for example a cyanate or an alkyl or aryl isocyanate, typically in the presence of a suitable base. Alternatively a suitable intermediate such as the chloroformate, succinimido carbonate, or imidazolocarbonyl derivative of a quinazoline of Formula I in which R¹ is hydroxy may be generated, for example by treatment of said derivative with phosgene (or a phosgene equivalent), disuccinimidocarbonate, or carbonyldiimidazole. The resulting intermediate may then be reacted with an appropriate amine or substituted amine to produce the desired carbamoyl derivatives.

For the production of quinazoline derivatives of Formula I wherein R¹ is aminocarbonyl or a substituted aminocarbonyl, the aminolysis of a suitable intermediate derived from a quinazoline of Formula I in which R¹ is carboxy is preferred.

The activation and coupling of a Formula I compound wherein R¹ is carboxy may be performed by a variety of methods known to those skilled in the art. Suitable methods include activation of the carboxyl as an acid halide, azide, symmetric or mixed anhydride, or active ester of appropriate reactivity for coupling with the desired amine. Examples of such types of intermediates and their production and use in couplings with amines may be found extensively in the literature; for example M. Bodansky and A. Bodansky, "The Practice of Peptide Synthesis", Springer-Verlag, New York, 1984.

The resulting Formula I compounds may be isolated and purified by standard methods, such as solvent removal and recrystallization or chromatography, if desired.

The starting materials for the above described reaction schemes (e.g., amines, quinazolines, amine protecting groups) are readily available or can be easily synthesized by those skilled in the art using conventional methods of organic synthesis. For example, the preparation of 2,3-dihydro-1,4-benzoxazine derivatives are described in R. C. Elderfield, W.H. Todd, S. Gerber, Ch. 12 in "Heterocyclic Compounds", Vol. 6, R. C. Elderfield ed., John Wiley and Sons, Inc., N.Y., 1957. Substituted 2,3-dihydro-benzothiazinyl compounds are described in R.C. Elderfield and E.E. Harris, Ch. 13 in Volume 6 of the Elderfield "Heterocyclic Compounds" book. The synthesis of 1,2,3,4-tetrahydroquinolines and their quinoline precursors are described in for example, "The Chemistry of Heterocyclic Compounds", Vol. 32, Parts 1, 2 and 3, G. Jones, ed., John Wiley and Sons, N.Y., 1977. Alkyl and aryl-substituted 1,2,3,4-tetrahydroquinolines were

typically prepared by the catalytic hydrogenation of the appropriately substituted quinolines using $\text{Pt}_2\text{O}/\text{H}_{2(g)}$ in MeOH (for example by the procedure of M. Honel and F. W. Vierhapper, J. Chem. Soc., Perkin I 1980, 1933-1939). The synthesis of substituted 2,3,4,5-tetrahydro-1H-benzo(b)azepines is described in G.R. Proctor, Ch. II, Vol.43, "The
5 Chemistry of Heterocyclic Compounds", Part I, A. Rosowsky, ed., Wiley Interscience, N.Y. 1984. Certain substituted 2,3,4,5-tetrahydro-1H-1-benzo[b]azepin-2-ones and 1,2,3,4,5,6-hexahydro-1-benzo[b]azocin-2-ones which are readily reduced to the corresponding 2,3,4,5-tetrahydro-1H-benzo[b]azepines and 1,2,3,4,5,6-hexahydro-1-benzo-[b]azocines, respectively are described in E.C. Horning et al, J. Am. Chem. Soc.
10 74, 5153 (1952), and R. Huisgen et al, Liebigs Ann. Chem. 586, 30 (1954).

In addition, the following general description in conjunction with Reaction Scheme I and the Preparations (which can be analogized therefrom) are provided as an additional aid to the preparation of the indoline based amines.

Thus, according to Scheme I the desired Formula II, III, IV or V indoline based
15 compounds may be conveniently prepared by reduction of the corresponding Formula IX indole based compounds (the dotted line circles refer to the fused monocyclic and bicyclic moieties of Formulas III, IV and V).

In general, the Formula IX compounds bearing aprotic R^2 or R^3 substituents are treated with ZnBH_4 (prepared from ZnCl_2 and NaBH_4 according to W.J. Gensler et al.,
20 J. Am. Soc. 82, 6074-6081 (1960)) in an ethereal solvent such as diethyl ether at a temperature of about 10°C to about 40°C , preferably at ambient. Such treatment is described in H. Korsuki et al., Heterocycles 26, 1771-1774 (1987). Alternatively, the Formula IX compounds may be treated with a borane/pyridine complex (or other borane/tertiary amine complex) in the absence of solvent, or presence of solvent, such
25 as tetrahydrofuran at a temperature of about 10°C to about 30°C , preferably at ambient, followed by treatment of the mixture with an acid such as hydrochloric acid, trifluoroacetic acid or acetic acid to provide compounds of Formula II, III, IV or V.

The desired Formula IX compounds wherein p is one or two may be prepared from the appropriate Formula XIV compound via a Fisher Indole synthesis or
30 modification thereof ("The Fischer Indole Synthesis", B. Robinson, Wiley Interscience, N.Y., 1982; or alternatively U. Pindur, R. Adam, J. Het. Chem. 25, 1-8 (1988) and references therein).

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The Formula IX indoles wherein p is zero may typically be prepared from the Formula XII aniline-type compounds from either of two routes: via the Formula X compounds or the Formula XI compounds. However, the route via Formula XI compound is not preferred for preparation of nitro or carboalkoxy substituted indoles.

5 Thus, the desired Formula IX compound may be prepared from the appropriate Formula X compound (e.g., isatins, oxindoles) by reduction, or from the appropriate Formula XI compound via a reductive cyclization. In general the Formula X compound is treated with borane in an ethereal solvent such as tetrahydrofuran at a temperature of about 0°C to about 30°C, preferably ambient. Generally the Formula XI compound is
10 treated with sodium borohydride in an ethereal solvent such as dioxane at a temperature of about 20°C to about 100°C, preferably reflux.

The desired Formula X isatin compound may be prepared from the appropriate Formula XII compound by combination with chloral hydrate and hydroxylamine followed by an acid catalyzed cyclization, such process being adapted from Org. Syn., Coll. Vol.
15 I, 327-330.

The desired Formula XI compound may be prepared from the appropriate Formula XII compound by a Lewis acid catalyzed ortho-acylation. The typical preparation is adapted from T. Sugasawa et al., J. Org. Chem. 44 (4), 578-586 (1979). In general, the Formula XII compound is reacted with 2-chloroacetonitrile in the
20 presence of boron trichloride and an auxiliary acid catalyst such as aluminum chloride, typically in an aromatic solvent such as xylene, toluene or chlorobenzene at a temperature of about 50°C to about reflux.

The desired Formula XII aminoaromatic compounds may be prepared from the appropriate corresponding nitroaromatic compounds by various reductive methods
25 (such as those given above).

Alternatively, some of the desired Formula II, III, IV or V indoline-based compounds may be prepared from other of the above described indoline-based compounds by further modification prior to combination with the quinazoline moieties of Formula I.

30 For example, the appropriately substituted desired 5-hydroxyindole may be prepared from the corresponding indolines by hydroxylation according to an adaptation of the procedure of H.J. Teuber and G. Staiger, Chem. Ber. 89, 489-508 (1956) followed by reduction to achieve the corresponding 5-hydroxyindoline. Generally, potassium

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nitrosodisulfonate in aqueous phosphate buffer is added to the appropriately substituted indoline in acetone at neutral pH at a temperature of about 0°C to about 25°C to produce the 5-hydroxyindole derivative, which may be subsequently reduced with borane/pyridine/aqueous HCl to afford the 5-hydroxyindoline.

5 The appropriately substituted desired bromoindolines (e.g., in the 4- or 6-position) may be prepared from the corresponding indolines by bromination analogous to the procedure described by: Y. Miyake and Y. Kikugawa, J. Het. Chem. 20, 349-352 (1983). This procedure may also be utilized for brominations of other larger rings (e.g., 1,2,3,4-tetrahydroquinolines, 2,3,4,5-tetrahydro-1H-benzo[b]azepines and 1,2,3,4,5,6-
10 hexahydro-benzo[b]azocines, particularly in the 5/7, 6/8, and 7/9-positions). Generally, the appropriately substituted indoline is reacted with bromine in the presence of a halophile such as silver sulfate under strongly acidic conditions at 0°C to 25°C.

In addition, certain indolines with or without 3-alkyl substituents may conveniently be prepared from the appropriate 2-(2-halophenyl)alkylamines according
15 to the German patent application DE 3424900A1.

In addition, hydroxyalkylindolines can be prepared by reduction of the appropriate carboxylic acids or their esters, for example according to E. J. Corey et al, J. Am. Chem. Soc. 92 (8), 2476-2488 (1970).

The appropriately substituted desired alkyl, alkenyl or allylic substituted indolines
20 may be prepared from the corresponding trialkylsilyl-protected 4-, 5- or 6-haloindolines via a Nickel-phosphine catalyzed Grignard addition analogous to the general procedure described by K. Tamao et al., Bull. Chem. Soc. Japan 49, 1958-1969 (1976). Generally, the indoline is N-protected by reaction with tert-butyldimethylsilyltriflate in a halogenated solvent in the presence of a tertiary amine. The N-silylated halo-indoline is
25 subsequently reacted with the appropriate alkyl, alkenyl or allylic Grignard in an ethereal solvent in the presence of a suitable nickel-phosphine complex, typically [Ni(dppe)Cl₂]. Subsequent treatment with methanol containing a trace of acid such as trifluoroacetic acid, or with fluoride anion in a suitable solvent such as THF, liberates the desired indoline product.

30 In addition, the desired substituted alkenyl- or alkynyl- indolines may be prepared by the palladium-catalyzed vinylation or alkynylation of the appropriate 4-, 5-, 6- or 7- haloindoline, for example, according to references reviewed by V. N. Kalinin, Synthesis 1991, 413-432. For example, for alkynylindolines, generally the

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corresponding bromo- or iodoindoline in diethylamine is treated with an alkyl-, appropriately substituted alkyl, or trimethylsilylacetylene in the presence of catalytic amounts of CuI and Pd(PPh₃)₄ at reflux.

Further, in addition to the nonlimiting examples provided herein the preparation
5 of various indolines, indoles, oxindoles, and isatins useful as intermediates are further described in "Heterocyclic Compounds with Indole and Carbazole Systems", W. C. Sumpter and F. M. Miller, in Vol. 8 of "The Chemistry of Heterocyclic Compounds" Series, Interscience Publishers Inc., N.Y., 1954 and references contained therein.

Certain Formula I quinazolines can exist in solvated as well as unsolvated
10 forms such as, for example, hydrated forms. It is to be understood that the invention encompasses all such solvated as well as unsolvated forms which possess activity against hyperproliferative diseases.

A suitable pharmaceutically-acceptable salt of a quinazoline derivative of the invention is, for example, an acid-addition salt of a quinazoline derivative of the
15 invention which is sufficiently basic, for example an acid-addition salt with, for example, an inorganic or organic acid, for example, hydrochloric, hydrobromic, sulphuric, phosphoric, methanesulfonic, benzenesulfonic, trifluoroacetic, citric, lactic or maleic acid. In addition a suitable pharmaceutically-acceptable base-addition salt of a quinazoline derivative of the invention which is sufficiently acidic is an alkali
20 metal salt, for example a lithium, sodium or potassium salt; an alkaline earth metal salt, for example a calcium or magnesium salt; an ammonium salt; or a salt with an organic base which affords a physiologically-acceptable cation for example a salt with methylamine, dimethylamine, trimethylamine, piperidine, morpholine or tris-(2-hydroxyethyl)amine. All such salts are within the scope of this invention and they
25 can be prepared by conventional methods. For example, they can be prepared simply by contacting the acidic and basic entities, usually in a stoichiometric ratio, in either an aqueous, non-aqueous or partially aqueous medium, as appropriate. The salts are recovered either by filtration, by precipitation with a non-solvent, preferably an etheral or hydrocarbon solvent, followed by filtration, by evaporation of the
30 solvent, or, in the case of aqueous solutions, by lyophilization, as appropriate.

Some of the compounds of Formula I incorporate asymmetric carbon atoms. Diastereomeric mixtures can be separated into their individual diastereomers on the basis of their physical chemical differences by methods known per se., for example,

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by chromatography and/or fractional crystallization. Enantiomers can be separated by converting the enantiomeric mixtures into a diastereomeric mixture by reaction with an appropriate optically active compound (e.g., alcohol or acid), separating the diastereomers and converting (e.g., hydrolyzing) the individual diastereomers to the
5 corresponding pure enantiomer. Alternatively, enantiomers may be resolved by differential crystallizations as diastereomeric salts. All such isomers, including diastereomers and enantiomers are considered as part of the invention.

The compounds of this invention are potent inhibitors of the erbB family of oncogenic and protooncogenic protein tyrosine kinases such as epidermal growth
10 factor receptor (EGFR), erbB2, HER3, or HER4 and thus are all adapted to therapeutic use as antiproliferative agents (e.g., anticancer) in mammals, particularly humans. In particular, the compounds of this invention are therapeutants or prophylactics for the treatment of a variety of benign or malignant human tumors (renal, liver, kidney, bladder, breast, gastric, ovarian, colorectal, prostate, pancreatic,
15 lung, vulval, thyroid, hepatic carcinomas, sarcomas, glioblastomas, various head and neck tumors), and other noncancerous hyperplastic disorders such as benign hyperplasia of the skin (e.g., psoriasis) or prostate (e.g., BPH). Such activity against benign disorders can be determined by standard assays such as described in J. Invest. Dermatol. 98, 296-301 (1992). It is in addition expected that a quinazoline of
20 the present invention may possess activity against a range of leukemias and lymphoid malignancies.

The compounds of Formula I also potentiate responses to conventional cancer chemotherapies and radiotherapy in a dose and schedule-dependent manner based upon the substantial synergy observed between neutralizing anti-EGFR
25 antibodies and conventional chemotherapeutants (J. Baselga et al., J. Nat. Cancer Inst. 85, 1327-1333 (1993); Z. Fan et al., Cancer. Res. 53, 4637-4642 (1993)).

The compounds of Formula I may also be expected to be useful in the treatment of additional disorders in which aberrant expression, ligand/receptor interactions, activation, or signalling events related to various protein tyrosine
30 kinases, whose activity is inhibited by the agents of Formula I, are involved.

Such disorders may include those of neuronal, glial, astrocytal, hypothalamic, and other glandular, macrophagal, epithelial, stromal, and blastocoelic nature in which aberrant function, expression, activation or signalling of the erbB tyrosine

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kinases may be involved. In addition, compounds of Formula I may have therapeutic utility in inflammatory, angiogenic and immunologic disorders involving both identified and as yet unidentified tyrosine kinases which are inhibited by compounds of Formula I.

- 5 The in vitro activity of these compounds in inhibiting the receptor tyrosine kinase (and thus subsequent proliferative response, e.g., cancer) may be determined by a procedure as detailed below.

- Activity of compounds of Formula I in vitro can be determined by the amount of inhibition of the phosphorylation of an exogenous substrate (e.g., Lys₃ - Gastrin or polyGluTyr (4:1) random copolymer (I. Posner et. al., J. Biol. Chem. 267 (29), 10 20638-47 (1992)) on tyrosine by epidermal growth factor receptor kinase by a test compound relative to a control. Affinity purified, soluble human EGF receptor (96 ng) is obtained according to the procedure in G. N. Gill, W. Weber, Methods in Enzymology 146, 82-88 (1987) from A431 cells (American Type Culture Collection, 15 Rockville, MD) and preincubated in a microfuge tube with EGF (2 μ g/ml) in phosphorylation buffer + vanadate (PBV: 50 mM HEPES, pH 7.4; 125 mM NaCl; 24 mM MgCl₂; 100 μ M sodium orthovanadate), in a total volume of 10 μ l, for 20-30 minutes at room temperature. The test compound, dissolved in DMSO, is diluted in PBV, and 10 μ l is mixed with the EGF receptor /EGF mix, and incubated for 10-30 20 minutes at 30°C. The phosphorylation reaction is initiated by addition of 20 μ l ³³P-ATP/ substrate mix (120 μ M Lys₃-Gastrin (sequence in single letter code for amino acids, KKKGPWLEEEEEAYGWLDF), 50 mM Hepes pH 7.4, 40 μ M ATP, 2 μ Ci γ -[³³P]-ATP) to the EGFr/EGF mix and incubated for 20 minutes at room temperature. The reaction is stopped by addition of 10 μ l stop solution (0.5 M EDTA, pH 8; 2mM ATP) 25 and 6 μ l 2N HCl. The tubes are centrifuged at 14,000 RPM, 4°C, for 10 minutes. 35 μ l of supernatant from each tube is pipetted onto a 2.5 cm circle of Whatman P81 paper, bulk washed four times in 5% acetic acid, 1 liter per wash, and then air dried. This results in the binding of substrate to the paper with loss of free ATP on washing. The [³³P] incorporated is measured by liquid scintillation counting.
- 30 Incorporation in the absence of substrate (e.g., lys₃-gastrin) is subtracted from all values as a background and percent inhibition is calculated relative to controls without test compound present.

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Activity of compounds of Formula I in vivo can be determined by the amount of inhibition of tumor growth by a test compound relative to a control. The tumor growth inhibitory effects of various compounds are measured according to the methods of Corbett, T. H., et al. "Tumor Induction Relationships in Development of Transplantable Cancers of the Colon in Mice for Chemotherapy Assays, with a Note on Carcinogen Structure", Cancer Res., **35**, 2434-2439 (1975) and Corbett, T. H., et al., "A Mouse Colon-tumor Model for Experimental Therapy", Cancer Chemother. Rep. (Part 2), **5**, 169-186 (1975), with slight modifications. Tumors are induced in the left flank by s.c. injection of 1×10^6 log phase cultured tumor cells (human MDA-MB-468 breast or human HN5 head and neck carcinoma cells) suspended in 0.10 ml RPMI 1640. After sufficient time has elapsed for the tumors to become palpable (2-3 mm in diameter) the test animals (athymic mice) are treated with compound (formulated by dissolution in DMSO typically at a concentration of 50 to 100 mg/mL followed by 1:9 dilution into 0.1% Pluronic® P105 in 0.9% saline) by the intraperitoneal (ip) or oral (po) routes of administration twice daily (i.e., every 12 hours) for 5 consecutive days. In order to determine a tumor growth inhibition, the tumor is measured in millimeters with Vernier calipers across two diameters and the tumor size (mg) is calculated using the formula: Tumor weight (TuW) = $(\text{length} \times [\text{width}]^2)/2$, according to the methods of Geran, R.I., et al. "Protocols for Screening Chemical Agents and Natural Products Against Animal Tumors and Other Biological Systems", Third Edition, Cancer Chemother. Rep., **3**, 1-104 (1972). Results are expressed as percent inhibition, according to the formula: Inhibition (%) = $(\text{TuW}_{\text{control}} - \text{TuW}_{\text{test}})/\text{TuW}_{\text{control}} \times 100\%$. The flank site of tumor implantation provides reproducible dose/response effects for a variety of chemotherapeutic agents, and the method of measurement (tumor diameter) is a reliable method for assessing tumor growth rates.

Administration of the compounds of this invention can be via any method which enables delivery of the compounds to the site of action (e.g., cancer cells). These methods include oral routes, intraduodenal routes, parenteral injection (including intravenous, subcutaneous, intramuscular, intravascular or infusion), topical administration, etc.

The amount of compound of this invention administered will, of course, be dependent on the subject being treated, on the severity of the affliction, on the

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manner of administration and on the judgment of the prescribing physician. However an effective dosage is in the range of approximately 0.1-100 mg/kg, preferably 1 to 35 mg/kg in single or divided doses. For an average 70kg human, this would amount to 0.05 to 7 g/day, preferably 0.2 to 2.5 g/day. For topical
5 administration (e.g., for psoriasis) a suitable formulation would include 0.01% to 5% of a compound of this invention, preferably 0.05% to 0.5%. Preferably the topical administration is applied directly to the site of affliction.

The pharmaceutical composition of the invention may, for example, be in a form suitable for oral administration as a tablet, capsule, pill, powder, sustained
10 release formulations, solution, suspension, for parenteral injection as a sterile solution, suspension or emulsion, for topical administration as an ointment or cream or for rectal administration as a suppository. The pharmaceutical composition may be in unit dosage forms suitable for single administration of precise dosages. The pharmaceutical compositions will include a conventional pharmaceutical carrier or
15 excipient and a compound according to the invention as an active ingredient. In addition, it may include other medicinal or pharmaceutical agents, carriers, adjuvants, etc.

Pharmaceutical compositions for non-topical administration according to the invention may contain 0.1%-95% of the compound, preferably 1%-70%. In any
20 event, the composition or formulation to be administered will contain a quantity of a compound according to the invention in an amount effective to alleviate or reduce the signs in the subject being treated, i.e., proliferative disorders, over the course of the treatment.

Exemplary parenteral administration forms include solutions or suspensions
25 of a compound according to the invention Formula I in sterile aqueous solutions, for example aqueous propylene glycol or dextrose solutions are employed. Such dosage forms can be suitably buffered, if desired.

Suitable pharmaceutical carriers include inert diluents or fillers, water and various organic solvents. These pharmaceutical compositions can, if desired,
30 contain additional ingredients such as flavorings, binders, excipients and the like. Thus for oral administration, tablets containing various excipients, such as citric acid can be employed, together with various disintegrants such as starch, alginic acid and certain complex silicates and with binding agents such as sucrose, gelatin and

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acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often useful for tableting purposes. Solid compositions of a similar type may also be employed in soft and hard filled gelatin capsules. Preferred materials therefore include lactose or milk sugar and high molecular weight

5 polyethylene glycols. When the aqueous suspensions or elixirs are desired for oral administration the essential active ingredient therein may be combined with various sweetening or flavoring agents, coloring matters or dyes and, if desired, emulsifying agents or suspending agents, together with diluents such as water, ethanol, propylene glycol, glycerin, or combinations thereof.

10 Methods of preparing various pharmaceutical compositions with a certain amount of active ingredient are known, or will be apparent in light of this disclosure, to those skilled in this art. For examples, see Remington's Pharmaceutical Sciences., Mack Publishing Company, Easter, Pa., 15th Edition (1975).

The anticancer treatment described above may be applied as a sole therapy
15 or may involve, in addition to the quinazoline derivative of the invention, one or more other antitumor substances or radiotherapy. Such conjoint treatment may be achieved by way of the simultaneous, sequential, cyclic or separate dosing of the individual components of the treatment.

It should be understood that the invention is not limited to the particular
20 embodiments shown and described herein, but that various changes and modifications may be made without departing from the spirit and scope of this novel concept as defined by the following claims.

EXAMPLES

Analytical reversed-phase HPLC (anal. RP18-HPLC) was performed by
25 injecting samples dissolved in a water-miscible solvent onto a Perkin-Elmer Pecosphere® 3X3C cartridge column (3mm X 3cm, C18; available from Perkin Elmer Corp., Norwalk, CT 06859) preceded by a Brownlee RP-8 Newguard precolumn (7 micron, 3.2mm X 15mm, available from Applied Biosystems Inc. San Jose, CA 95134) both of which were previously equilibrated in pH4.50, 200 mM NH₄OAc
30 buffer. Samples were eluted using a linear gradient of 0-100% MeCN/pH4.50, 200 mM NH₄OAc over 10 minutes with a flow rate of 3.0 mL/min. Chromatograms were generated over the range 240-400nm using a Diode array detector.

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Gas Chromatography-Mass Spectrometry was carried out on a Hewlett Packard Instrument (5890 Series II) equipped with a 12m HP-1 Column (200 μ M i.d.). A temperature gradient from 133°C (0-0.10 min.) to 310°C at a heating rate of 18°C/min with an He_(g) carrier was employed to separate components with peak
5 detection through the use of a 5971 Series Mass Selective Detector.

Example 1

4-(6-Chloro-2,3-dihydro-indol-1-yl)-7,8-dihydro-[1,4]dioxino [2,3-g]quinazoline

To 6-chloroindoline (52mg, 0.339 mmol) and pyridine (23.3mg, 0.294 mmol)
10 in i-PrOH (3 mL) was added 4-chloro-6,7-(ethylenedioxy)quinazoline (65 mg, 0.294 mmol). The mixture was heated to reflux under dry N_{2(g)} for 16 hours and then concentrated in vacuo. The residue was partitioned between CHCl₃ and saturated aqueous NaHCO₃, and the organic phase was washed with brine, dried over Na₂SO_{4 (s)}, and concentrated in vacuo. The residue was flash chromatographed on
15 silica using 30% acetone/hexanes to afford 84mg of 4-(6-chloro-2,3-dihydro-indol-1-yl)-7,8-dihydro-[1,4]dioxino [2,3-g]quinazoline as its free-base (M.P. 209-211°C; GC/MS: 339 (M⁺); anal. RP18-HPLC RT: 5.02 min).

Example 2

4-(6-Fluoro-2,3-dihydro-indol-1-yl)-6,7-dimethoxy-quinazoline

To 6-fluoroindoline (274 mg, 2.0 mmol) in dry i-PrOH (10mL) was added 4-chloro-6,7-dimethoxy-quinazoline (225mg, 1.0 mmol). The mixture was refluxed for 16 hours under an atmosphere of dry N_{2 (g)} and then the solvent was removed in vacuo. The residue was partitioned between CHCl₃ and 1M NaOH, and the organic phase was washed with brine, dried over Na₂SO_{4 (s)} and concentrated in vacuo. The
25 residue (535mg) was purified by flash chromatography on silica using 80%EtOAc/CH₂Cl₂ to yield 4-(6-fluoro-2,3-dihydro-indol-1-yl)-6,7-dimethoxy-quinazoline as its free base (293mg) (GC/MS: 325 (M⁺); LC-MS: 326 (MH⁺); anal. RP18-HPLC RT: 4.37 min.).

For conversion to its HCl salt this product (293mg) was dissolved in minimal
30 CHCl₃/Et₂O and a 1M solution of HCl in Et₂O (1.0 mL) was added dropwise with stirring. The resulting yellow HCl salt which precipitated was filtered out, washed with dry Et₂O and pet. ether, and dried in vacuo to constant mass (310mg; M.P. 220°C (dec)).

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Example 34-(6-Chloro-2,3-dihydro-indol-1-yl)-6,7-dimethoxy-quinazoline

To 6-chloroindoline hydrochloride (100 mg, 0.526 mmol) and pyridine (0.957 mmol, 77 μ L) in dry i-PrOH (8 mL) was added 4-chloro-6,7-dimethoxy-quinazoline (107mg, 0.478 mmol). The mixture was refluxed for 2 hours under an atmosphere of dry N₂ (g) and then the solvent was removed in vacuo. The residue was partitioned between CHCl₃ and 1M NaOH, and the organic phase was washed with brine, dried over Na₂SO₄ (s), and concentrated in vacuo. The residue (171 mg) was purified by flash chromatography on silica using 80%EtOAc/CH₂Cl₂ to yield 4-(6-chloro-2,3-dihydro-indol-1-yl)-6,7-dimethoxy-quinazoline as its free base (148 mg) (M.P. 229-230°C; LC-MS: 342 (MH⁺); anal. RP18-HPLC RT: 4.38 min.).

Example 44-(2,3-Dihydro-indol-1-yl)-6,7-dimethoxy-quinazoline

Utilizing a procedure analogous to that described in Example 2, this product was prepared in 94% yield from indoline (2 eq.) and 4-chloro-6,7-dimethoxy-quinazoline (1.0 eq) in i-PrOH. (M.P. 162-163°C; LC-MS: 308 (MH⁺); anal. RP18-HPLC RT: 4.11 min.).

Example 56,7-Dimethoxy-4-(2-methyl-2,3-dihydro-indol-1-yl)-quinazoline

Utilizing a procedure analogous to that described in Example 1, this product was prepared in 91% yield from 2-methyl-indoline (1.1 eq.) and 4-chloro-6,7-dimethoxy-quinazoline (1.0 eq) in i-PrOH. (M.P. 154-156.5°C; GC-MS: 321 (M⁺); anal. RP18-HPLC RT: 4.93 min.).

Example 64-(4-Chloro-2,3-dihydro-indol-1-yl)-6,7-dimethoxy-quinazoline

Utilizing a procedure analogous to that described in Example 2, this product was prepared in 92% yield from 4-chloro-indoline (2 eq.) and 4-chloro-6,7-dimethoxy-quinazoline (1.0 eq) in i-PrOH. (M.P. 172-179°C (dec); LC-MS: 342 (MH⁺); anal. RP18-HPLC RT: 4.60 min.).

Example 74-(3,4-Dihydro-2H-quinolin-1-yl)-6,7-dimethoxy-quinazoline

Utilizing a procedure analogous to that described in Example 2, this product was prepared in 91% yield from 1,2,3,4-tetrahydroquinoline (2 eq.) and 4-chloro-6,7-

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dimethoxy-quinazoline (1.0 eq) in *i*-PrOH. (M.P. 130-131°C ; LC-MS: 322 (MH⁺); anal. RP18-HPLC RT: 4.08 min.).

Example 8

6,7-Dimethoxy-4-(6-methyl-3,4-dihydro-2H-quinolin-1-yl)-quinazoline

5 Utilizing a procedure analogous to that described in Example 2, this product was prepared in 94% yield from 6-methyl-1,2,3,4-tetrahydroquinoline (2 eq.) and 4-chloro-6,7-dimethoxy-quinazoline (1.0 eq) in *i*-PrOH. (M.P. 147-148°C ; LC-MS: 336 (MH⁺); anal. RP18-HPLC RT: 4.51 min.).

Example 9

10 6,7-Dimethoxy-4-(7-trifluoromethyl-3,4-dihydro-2H-quinolin-1-yl)-quinazoline

Utilizing a procedure analogous to that described in Example 2, this product was prepared in 66% recrystallized yield (from CHCl₃/hexane) from 6-trifluoromethyl-1,2,3,4-tetrahydroquinoline (2 eq.) and 4-chloro-6,7-dimethoxy-quinazoline (1.0 eq) in *i*-PrOH. (M.P. 184-185°C ; LC-MS: 390 (MH⁺); anal. RP18-HPLC RT: 5.10 min.).

15

Example 10

4-(6-Chloro-2,3-dihydro-indol-1-yl)-6,7-diethoxy-quinazoline

Utilizing a procedure analogous to that described in Example 1, this product was prepared in 99% yield from 6-chloro-indoline (1.1 eq.) and 4-chloro-6,7-diethoxy-quinazoline (1.0 eq) in *i*-PrOH. (M.P. 159-163°C; GC-MS: 369 (M⁺); anal. RP18-HPLC RT: 5.25 min.).

20

Example 11

7-Butoxy-4-(6-chloro-2,3-dihydro-indol-1-yl)-6-methoxy-quinazoline

Utilizing a procedure analogous to that described in Example 1, this product was prepared in 43% yield from 6-chloro-indoline (1.1 eq.) and 7-butoxy-4-chloro-6-methoxy-quinazoline (1.0 eq) in *i*-PrOH. (M.P. 126-132°C; GC-MS: 383 (M⁺); anal. RP18-HPLC RT: 6.22 min.).

25

Example 12

6,7-Dimethoxy-4-(6-methyl-2,3-dihydro-indol-1-yl)-quinazoline hydrochloride

Utilizing a procedure analogous to that described in Example 1, this product was prepared in 88% yield from 6-methyl-indoline (1.1 eq.) and 4-chloro-6,7-dimethoxy-quinazoline (1.0 eq) in *i*-PrOH. The HCl salt was generated from the purified free base according to the procedure given in Example 2 (M.P. 231-232°C; LC-MS: 322 (MH⁺); anal. RP18-HPLC RT: 4.32 min.).

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Example 136,7-Dimethoxy-4-(4-methyl-2,3-dihydro-indol-1-yl)-quinazoline

Utilizing a procedure analogous to that described in Example 1, this product was prepared in 94% yield from 4-methyl-indoline (1.1 eq.) and 4-chloro-6,7-dimethoxy-quinazoline (1.0 eq) in i-PrOH. (M.P. 174-175°C; LC-MS: 322 (MH⁺); anal. RP18-HPLC RT: 4.85 min.).

Examples 14 & 15

6,7-Dimethoxy-4-(cis-2,3-dimethyl-2,3-dihydro-indol-1-yl)-
quinazoline and 6,7-Dimethoxy-4-(trans-2,3-dimethyl
-2,3-dihydro-indol-1-yl)-quinazoline

These products were obtained as racemates following flash chromatography on silica in 55-65% EtOAc/hexanes in 65% & 15% yield, respectively, when prepared from a commercial mixture of cis/trans-2,3-dimethyl-indoline (1.1 eq.) and 4-chloro-6,7-dimethoxy-quinazoline (1.0 eq) in i-PrOH utilizing a procedure analogous to that described in Example 1. For the cis-isomer: M.P. 174-175°C; LC-MS: 336 (MH⁺); anal. RP18-HPLC RT: 5.15 min.; For the trans-isomer: LC-MS: 336 (MH⁺); anal. RP18-HPLC RT: 4.83 min.

Example 164-(6-Iodo-2,3-dihydro-indol-1-yl)-6,7-dimethoxy-quinazoline hydrochloride

Utilizing a procedure analogous to that described in Example 1, this product was prepared in 78% yield from 6-iodo-indoline (1.1 eq.) and 4-chloro-6,7-dimethoxy-quinazoline (1.0 eq) in i-PrOH. The HCl salt was generated from the purified free base according to the procedure given in Example 2 (M.P. >230°C; GC/MS: 433 (M⁺); anal. RP18-HPLC RT: 5.20 min.).

Example 174-(5-Fluoro-2,3-dihydro-indol-1-yl)-6,7-dimethoxy-quinazoline

Utilizing a procedure analogous to that described in Example 1, this product was prepared in 81% yield from 5-fluoro-indoline (1.1 eq.) and 4-chloro-6,7-dimethoxy-quinazoline (1.0 eq) in i-PrOH. (M.P. 190-191°C; LC-MS: 326 (MH⁺); anal. RP18-HPLC RT: 4.40 min.).

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Example 184-(6-Chloro-2,3-dihydro-indol-1-yl)-6,7,8-trimethoxy-quinazoline

Utilizing a procedure analogous to that described in Example 1, this product was prepared in 20% yield from 6-chloro-indoline (1.1 eq.) and 4-chloro-6,7,8-trimethoxy-quinazoline (1.0 eq) in i-PrOH. (M.P. 139-143°C; GC/MS: 371 (M⁺); anal. RP18-HPLC RT: 4.70 min.).

Example 194-(6-Benzyloxy-2,3-dihydro-indol-1-yl)-6,7-dimethoxy-quinazoline hydrochloride

Utilizing a procedure analogous to that described in Example 1, this product was prepared in 80% yield from 6-benzyloxy-indoline (1.1 eq.) and 4-chloro-6,7-dimethoxy-quinazoline (1.0 eq) in i-PrOH. The HCl salt was generated from the purified free base according to the procedure given in Example 2. (M.P. 249-250°C(dec); LC-MS: 414 (MH⁺); anal. RP18-HPLC RT: 5.01 min.).

Example 206,7-Dimethoxy-4-(6-methoxy-2,3-dihydro-indol-1-yl)-quinazoline hydrochloride

Utilizing a procedure analogous to that described in Example 1, this product was prepared in 91% yield from 6-methoxy-indoline (1.1 eq.) and 4-chloro-6,7-dimethoxy-quinazoline (1.0 eq) in i-PrOH. The HCl salt was generated from the purified free base according to a procedure analogous to that given in Example 2. (M.P. 246-247°C(dec); LC-MS: 338 (MH⁺); anal. RP18-HPLC RT: 4.27 min.).

Example 214-(6-Bromo-2,3-dihydro-indol-1-yl)-6,7-dimethoxy-quinazoline hydrochloride

Utilizing a procedure analogous to that described in Example 1, this product was prepared in 88% yield from 6-bromo-indoline (1.1 eq.) and 4-chloro-6,7-dimethoxy-quinazoline (1.0 eq) in i-PrOH. The HCl salt was generated from the purified free base according to a procedure analogous to that given in Example 2. (M.P. 245-248°C(dec); LC-MS: 386, 388 (MH⁺); anal. RP18-HPLC RT: 4.95 min.).

Example 224-(5-Chloro-2,3-dihydro-indol-1-yl)-6,7-dimethoxy-quinazoline

Utilizing a procedure analogous to that described in Example 1, this product was prepared in 92% yield from 5-chloro-indoline (1.1 eq.) and 4-chloro-6,7-dimethoxy-quinazoline (1.0 eq) in i-PrOH. (M.P. 190-191°C; GC/MS: 3.41 (M⁺); anal. RP18-HPLC RT: 4.58 min.).

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Example 236,7-Dimethoxy-4-(5-methyl-2,3-dihydro-indol-1-yl)-quinazoline

Utilizing a procedure analogous to that described in Example 1, this product was prepared in 94% yield from 5-methyl-indoline (1.1 eq.) and 4-chloro-6,7-dimethoxy-quinazoline (1.0 eq) in i-PrOH. (M.P. 180-181°C; GC/MS: 321 (M⁺); anal. RP18-HPLC RT: 4.37 min.).

Example 241-(6,7-Dimethoxy-quinazolin-4-yl)-2,3-dihydro-1H-indole-2-carboxylic acid methyl ester

DL-Indoline-2-carboxylic acid methyl ester (0.806g, 4.55 mmol) and pyridine (0.236 mL, 4.51 mmol) were added to a solution of 4-chloro-6,7-dimethoxy-quinazoline (1.01g, 4.50 mmol) in DMF (10mL) and the mixture was heated to 80°C for 4.5 hours. The product was isolated in 87% yield following extractive workup and flash chromatography as in Example 1. (M.P. 186-189.5°C; LC-MS: 366 (MH⁺); anal. RP18-HPLC RT: 4.28 min.).

Example 254-(3,4-Dihydro-2H-quinolin-1-yl)-6-methoxy-quinazoline

Utilizing a procedure analogous to that described in Example 2, this product was prepared in 59% yield from 1,2,3,4-tetrahydroquinoline (2 eq.) and 4-chloro-6-methoxy-quinazoline (1.0 eq) in EtOH. (M.P. 98°C ; LC-MS: 292 (MH⁺).

Example 266,7-Dimethoxy-4-(6-nitro-2,3-dihydro-indol-1-yl)-quinazoline

Utilizing a procedure analogous to that described in Example 1, this product was prepared in 91% yield from 6-nitro-indoline (1 eq.) and 4-chloro-6,7-dimethoxy-quinazoline (1.0 eq) in i-PrOH. (M.P. 275° C (dec); GC-MS: 352 (M⁺); anal. RP18-HPLC RT: 4.30 min.).

Example 274-(6-Bromo-5-fluoro-2,3-dihydro-indol-1-yl)-6,7-dimethoxy-quinazoline hydrochloride salt

Utilizing a procedure analogous to that described in Example 1, this product was prepared in 68% yield from 5-fluoro-6-bromo-indoline (1.1 eq.) and 4-chloro-6,7-dimethoxy-quinazoline (1.0 eq) in i-PrOH. (M.P. 258° C (dec); LC-MS: 404, 406 (MH⁺); anal. RP18-HPLC RT: 5.06 min.).

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Example 286,7-Dimethoxy-4-(7-methyl-2,3-dihydro-indol-1-yl)-quinazoline

Utilizing a procedure analogous to that described in Example 24, this product was prepared in 65% yield from 7-methyl-indoline (1 eq.), pyridine (2 eq.) and 4-chloro-6,7-dimethoxy-quinazoline (1.0 eq) in DMF. (M.P. 146-147° C; GC-MS: 321 (M⁺); anal. RP18-HPLC RT: 4.41 min.).

Example 29[1-(6,7-Dimethoxy-quinazolin-4-yl)-2,3-dihydro-1H-indol-2-yl]-methanol

Utilizing a procedure analogous to that described in Example 1, this product was prepared in 57% yield from 2-hydroxymethyl-indoline (1 eq.) and 4-chloro-6,7-dimethoxy-quinazoline (1.0 eq) in i-PrOH. (M.P. 145.5-147° C; LC-MS: 338 (MH⁺); anal. RP18-HPLC RT: 4.03 min.).

Example 301-(6,7-Dimethoxy-quinazolin-4-yl)-2,3-dihydro-1H-indol-6-ylamine

6,7-Dimethoxy-4-(6-nitro-2,3-dihydro-indol-1-yl)-quinazoline (0.50 g, 1.42 mmol; from Example 26) in MeOH (10 mL) with conc. HCl (1 mL) was hydrogenated for 18 hours under 45 psi of H_{2(g)} in the presence of 10% Pd-C (105 mg). Following filtration through a pad of Celite and concentration of the filtrate in vacuo, the residue was taken up in 10% i-PrOH/CHCl₃ and the organic phase washed successively with saturated NaHCO₃, 0.1 M disodium EDTA, and brine. The organic solution was dried over Na₂SO_{4(s)}, filtered and concentrated in vacuo to afford the product as a yellow solid (423 mg; M.P. 215-217.5°C; LC-MS: 323 (MH⁺); anal. RP-HPLC RT: 3.10 min).

Example 314-(6-Isothiocyanato-2,3-dihydro-indol-1-yl)-6,7-dimethoxy-quinazoline

To a solution of thiocarbonyl diimidazole (90 mg, 0.505 mmol) in CHCl₃ (1 mL) was added dropwise a solution of 1-(6,7-dimethoxy-quinazolin-4-yl)-2,3-dihydro-1H-indol-6-ylamine (163 mg, 0.506 mmol; from Example 30) in CH₃CN (8 mL) at 5-10°C over 2 hours. After stirring 4 hours at 5°C the solvent was removed in vacuo and the residue was flash chromatographed on silica (1% MeOH/CHCl₃) to afford 115 mg of the isothiocyanate product (M.P. 214-215°C; GC-MS: 364 (M⁺); anal. RP18-HPLC RT: 5.60 min.).

Example 326,7-Dimethoxy-4-(6-pyrrol-1-yl-2,3-dihydro-indol-1-yl)-quinazoline

To 1-(6,7-Dimethoxy-quinazolin-4-yl)-2,3-dihydro-1H-indol-6-ylamine (155 mg, 0.481 mmol, from Example 30) in glacial acetic acid (4 mL) was added 1,4-dimethoxy-tetrahydrofuran (72.3 μ L, 0.558 mmol). The mixture was heated to 90°C under dry N_{2(g)} for 4 hours and concentrated in vacuo. The residue was dissolved in CHCl₃ and washed with saturated aqueous NaHCO₃ (2X), and brine and the organic phase was dried over MgSO_{4(s)}, filtered and concentrated in vacuo. The residue was chromatographed on silica (50% acetone/hexanes) to afford 71 mg of the 6-pyrrolyl derivative. (M.P. 185-186° C; GC-MS: 372 (M⁺); anal. RP18-HPLC RT: 4.60 min.).

Examples 33 & 346,7-Dimethoxy-4-(trans-octahydro-indol-1-yl)-quinazoline & 6,7-Dimethoxy-4-(cis-octahydro-indol-1-yl)-quinazoline

Utilizing a procedure analogous to that described in Example 24, the title products were prepared from cis/trans-perhydroindole (1.1 eq.), triethylamine (1.1 eq.) and 4-chloro-6,7-dimethoxy-quinazoline (1.0 eq) in DMF. Isomers were resolved on silica using EtOAc as the eluant to afford 16% of the trans-isomer (M.P. 130-131° C; LC-MS: 314 (MH⁺); anal. RP18-HPLC RT: 4.05 min.) and 46% of the cis-isomer (M.P. 123-124° C; LC-MS: 314 (MH⁺); anal. RP18-HPLC RT: 3.89 min.).

Example 354-(6-Bromo-7-methyl-2,3-dihydro-indol-1-yl)-6,7-dimethoxy-quinazoline

Utilizing a procedure analogous to that described in Example 24, this product was prepared in 93% yield from 6-bromo-7-methyl-indoline (1.1 eq.), and 4-chloro-6,7-dimethoxy-quinazoline (1.0 eq) in DMF. (M.P. 240-242° C; LC-MS: 400, 402 (MH⁺); anal. RP18-HPLC RT: 5.13 min.). The hydrochloride salt was produced using procedures analogous to that as described for Example 2: M.P. 243-244° C.

Example 364-(4-Bromo-7-methyl-2,3-dihydro-indol-1-yl)-6,7-dimethoxy-quinazoline

Utilizing a procedure analogous to that described in Example 24, this product was prepared in 70% yield from 4-bromo-7-methyl-indoline (1.1 eq.), and 4-chloro-6,7-dimethoxy-quinazoline (1.0 eq) in DMF. (M.P. 223-225° C; LC-MS: 400, 402 (MH⁺); anal. RP18-HPLC RT: 5.23 min.).

Example 374-(6-Butyl-2,3-dihydro-indol-1-yl)-6,7-dimethoxy-quinazoline

Utilizing a procedure analogous to that described in Example 1, this product was prepared in 53% yield from 6-n-butyl-indoline (1.1 eq.), and 4-chloro-6,7-dimethoxy-quinazoline (1.0 eq) in *i*-PrOH. (M.P. 130-131° C; GC-MS: 363 (M⁺); anal. RP18-HPLC RT: 5.41 min.).

Example 386,7-Dimethoxy-4-(6-phenyl-2,3-dihydro-indol-1-yl)-quinazoline

Utilizing a procedure analogous to that described in Example 1, this product was prepared in 61% yield from 6-phenyl-indoline (1.1 eq.), and 4-chloro-6,7-dimethoxy-quinazoline (1.0 eq) in *i*-PrOH. (M.P. 175-177° C; GC-MS: 383 (M⁺); anal. RP18-HPLC RT: 6.03min.).

Example 395-(6,7-Dimethoxy-quinazolin-4-yl)-6,7-dihydro-5H-[1,3]dioxolo[4,5-f]indole

Utilizing a procedure analogous to that described in Example 1, this product was prepared in 93% yield from 6,7-dihydro-5H-[1,3]dioxolo[4,5-f]indole (1.1 eq.), and 4-chloro-6,7-dimethoxy-quinazoline (1.0 eq) in *i*-PrOH. (M.P. 225-228° C (dec); LC-MS: 352 (MH⁺); anal. RP18-HPLC RT: 3.91 min.).

Example 404-(6-Isopropyl-2,3-dihydro-indol-1-yl)-6,7-dimethoxy-quinazoline

Utilizing a procedure analogous to that described in Example 1, this product was prepared in 43% yield from 6-isopropyl-indoline (1.1 eq.), and 4-chloro-6,7-dimethoxy-quinazoline (1.0 eq) in *i*-PrOH. (M.P. 128-129° C ; LC-MS: 350 (MH⁺); anal. RP18-HPLC RT: 5.51 min.).

Example 416,7-Dimethoxy-4-(6-propyl-2,3-dihydro-indol-1-yl)-quinazoline

Utilizing a procedure analogous to that described in Example 1, this product was prepared in 43% yield from 6-propyl-indoline (1.1 eq.), and 4-chloro-6,7-dimethoxy-quinazoline (1.0 eq) in *i*-PrOH. (M.P. 140-141° C ; LC-MS: 350 (MH⁺); anal. RP18-HPLC RT: 5.73 min.).

Example 424-(6-Azido-2,3-dihydro-indol-1-yl)-6,7-dimethoxy-quinazoline

To 1-(6,7-dimethoxy-quinazolin-4-yl)-2,3-dihydro-1H-indol-6-ylamine (104 mg, 0.323 mmol; from Example 30) in 80% acetic acid/H₂O (8 mL) was added NaNO₂ (35 mg, 0.35 mmol) in H₂O(200 μ L) at 5°C. After stirring 10 min. at 5°C a solution of NaN₃ (22mg, 0.34 mmol) in H₂O(200 μ L) was added and the mixture was allowed to warm to 22°C and stirred for 1 hour. Following the removal of solvents by lyophilization the residue was dissolved in EtOAc and washed with saturated aqueous NaHCO₃ (2X), and brine, and the organic phase was dried over MgSO₄(s), filtered and concentrated in vacuo. The residue was chromatographed on silica (2% MeOH/CHCl₃) to afford 72 mg of the azide. (M.P. 184-186° C (dec); LC-MS: 349 (MH⁺); anal. RP18-HPLC RT: 4.70 min.).

Example 43[1-(6,7-Dimethoxy-quinazolin-4-yl)-2,3-dihydro-1H-indol-5-yl]-(1-methyl-heptyl)-amine

Utilizing a procedure analogous to that described in Example 1, this product was prepared in 96% yield from [2,3-dihydro-1H-indol-5-yl]-(1-methyl-heptyl)-amine (1.1 eq.), and 4-chloro-6,7-dimethoxy-quinazoline (1.0 eq) in *i*-PrOH. (M.P. 61-63° C; GC-MS: 434 (M⁺); anal. RP18-HPLC RT: 6.91 min.).

Example 446,7-Dimethoxy-4-(5-methoxy-2,3-dihydro-indol-1-yl)-quinazoline methanesulfonate salt

Utilizing a procedure analogous to that described in Example 1, this product was prepared in 95% yield from 5-methoxy-indoline (1.1 eq.), and 4-chloro-6,7-dimethoxy-quinazoline (1.0 eq) in *i*-PrOH. The free-base obtained following column chromatography on silica (45% acetone/hexanes) was dissolved in minimal CH₂Cl₂ and treated with 1eq. of methanesulfonic acid in CH₂Cl₂ followed by dilution with several volumes of ether to precipitate the mesylate salt which was filtered and dried in vacuo. (M.P. 285-292° C (dec); LC-MS: 338 (MH⁺); anal. RP18-HPLC RT: 3.82 min.).

Example 454-(5-Benzyloxy-2,3-dihydro-indol-1-yl)-6,7-dimethoxy-quinazoline

Utilizing a procedure analogous to that described in Example 1, this product was prepared in 90% yield from 5-benzyloxy-indoline (1.1 eq.), and 4-chloro-6,7-

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dimethoxy-quinazoline (1.0 eq) in *i*-PrOH. (M.P. 181-182° C ; LC-MS: 415 (MH⁺); anal. RP18-HPLC RT: 4.78 min.).

Example 46

6,7-Dimethoxy-4-(6-pyrrolidin-1-yl-2,3-dihydro-indol-1-yl)-quinazoline

5 To 1-(6,7-dimethoxy-quinazolin-4-yl)-2,3-dihydro-1H-indol-6-ylamine (103 mg, 0.320 mmol; from Example 30) in DMF (4 mL) was added 1,4-dibromo-butane (42 μ L, 0.352 mmol) and pyridine (34 μ L, 0.64 mmol) and the mixture was heated to 110°C for 36 hours under N_{2(g)}. The mixture was diluted with saturated aqueous NaHCO₃ and extracted with EtOAc/Et₂O (1:1) and the organic phase was washed
10 with water and brine, dried over Na₂SO_{4(s)}, filtered and concentrated in vacuo. The residue was chromatographed on silica (4% MeOH/CHCl₃) to afford 20 mg of product. (M.P. 198-205° C (dec); GC-MS: 376 (M⁺); anal. RP18-HPLC RT: 5.05 min.).

Example 47

15 4-(6-Chloro-5-fluoro-2,3-dihydro-indol-1-yl)-6,7-dimethoxy-quinazoline
methanesulfonate salt

6-Chloro-5-fluoro-indoline (157 mg, 0.915 mmol), pyridine (48 μ L), and 4-chloro-6,7-dimethoxy-quinazoline (210 mg, 0.895 mmol) were heated to 120°C in N-methyl-pyrrolidin-2-one (2 mL) under N_{2(g)} for 36 hours. The mixture was partitioned
20 between EtOAc and saturated aqueous NaHCO₃, and the organic phase was washed several times with water and brine, dried over MgSO_{4(s)}, filtered and concentrated in vacuo. The residue was flash chromatographed on silica using 40% acetone/hexanes to elute the product (90 mg) which was converted to the methanesulfonate salt as described in Example 44. (M.P. 261-264° C; LC-MS: 360
25 (MH⁺); anal. RP18-HPLC RT: 4.31 min.).

Example 48

1-(6,7-Dimethoxy-quinazolin-4-yl)-2,3-dihydro-1H-indol-5-ol methanesulfonate salt

Utilizing a procedure analogous to that described in Example 1 (with conversion to the methanesulfonate salt analogous to that described in Example
30 44), this product was prepared in 90% yield from 5-hydroxy-indoline (1.1 eq.), and 4-chloro-6,7-dimethoxy-quinazoline (1.0 eq) in *i*-PrOH. (M.P. 245-250° C (dec); LC-MS: 324 (MH⁺); anal. RP18-HPLC RT: 2.76 min.).

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Example 491-(6,7-Dimethoxy-quinazolin-4-yl)-6-methyl-2,3-dihydro-1H-indol-5-ol
methanesulfonate salt

Utilizing a procedure analogous to that described in Example 1 (with
5 conversion to the methanesulfonate salt analogous to that described in Example
44), this product was prepared in 45% yield from 5-hydroxy-6-methyl-indoline (1.1
eq.), and 4-chloro-6,7-dimethoxy-quinazoline (1.0 eq) in *i*-PrOH. (For Free base:
M.P. 230°C; For salt: M.P. 290° C (dec); LC-MS: 338 (MH⁺); anal. RP18-HPLC RT:
3.11 min.).

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Example 504-(6,7-Dimethyl-2,3-dihydro-indol-1-yl)-6,7-dimethoxy-
quinazoline methanesulfonate salt

Utilizing a procedure analogous to that described in Example 47 (with
conversion to the methanesulfonate salt analogous to that described in Example
15 44), this product was prepared in 92% yield from 6,7-dimethyl-indoline (1.1 eq.), and
4-chloro-6,7-dimethoxy-quinazoline (1.0 eq) in N-methyl-pyrrolidin-2-one. (M.P. 232-
237° C; GC-MS: 335 (M⁺); anal. RP18-HPLC RT: 4.44 min.).

Example 511-(6,7-Dimethoxy-quinazolin-4-yl)-2,3,4,5-tetrahydro-1H-benzo[b]azepine
methanesulfonate salt

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Utilizing a procedure analogous to that described in Example 47 (with
conversion to the methanesulfonate salt analogous to that described in Example
44), this product was prepared in 92% yield from 2,3,4,5-tetrahydro-1H-
benzo[b]azepine (1.1 eq.), and 4-chloro-6,7-dimethoxy-quinazoline (1.0 eq) in N-
25 methyl-pyrrolidinone. (M.P. 218.2-218.6° C; LC-MS: 336 (MH⁺); anal. RP18-HPLC
RT: 4.46 min.).

Example 526,7-Dimethoxy-4-(5-nitro-2,3-dihydro-indol-1-yl)-quinazoline

Utilizing a procedure analogous to that described in Example 47, the adduct
30 from 5-nitro-indoline (1.1 eq.), and 4-chloro-6,7-dimethoxy-quinazoline (1.0 eq) in N-
methyl-pyrrolidinone was isolated in 42% yield (M.P. 245-249°C (dec); LC-MS: 353
(MH⁺); anal. RP18-HPLC RT: 3.95 min.).

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Example 534-(5-Azido-2,3-dihydro-indol-1-yl)-6,7-dimethoxy-quinazoline

A solution of 1-(6,7-dimethoxy-quinazolin-4-yl)-2,3-dihydro-1H-indol-5-ylamine (155 mg, 0.481 mmol; from Example 83 as the free-base) in 80% AcOH/H₂O (10 mL) was treated using procedures analogous to that described in Example 42 to afford the azide derivative in 47% isolated yield. (M.P. 159-165° C (dec); LC-MS: 349 (MH⁺); anal. RP18-HPLC RT: 4.93 min.).

Example 546-Chloro-1-(6,7-dimethoxy-quinazolin-4-yl)-2,3-dihydro-1H-indol-5-ol

10 methanesulfonate salt

Utilizing a procedure analogous to that described in Example 1 (with conversion to the methanesulfonate salt analogous to that described in Example 44), this product was prepared in 49% yield from 6-chloro-5-hydroxy-indoline (1.1 eq.), and 4-chloro-6,7-dimethoxy-quinazoline (1.0 eq) in i-PrOH. (M.P. 268-275° C; LC-MS: 358 (MH⁺); anal. RP18-HPLC RT: 3.45 min.).

Example 551-(6,7-Dimethoxy-quinazolin-4-yl)-7-methyl-2,3-dihydro-1H-indol-5-ol

methanesulfonate salt

Utilizing a procedure analogous to that described in Example 1 (with conversion to the methanesulfonate salt analogous to that described in Example 44), this product was prepared in 73% yield from 5-hydroxy-7-methyl-indoline (1.1 eq.), and 4-chloro-6,7-dimethoxy-quinazoline (1.0 eq) in i-PrOH. (M.P. 145-146° C (dec); LC-MS: 338 (MH⁺); anal. RP18-HPLC RT: 3.20 min.).

Example 561-(6,7-Dimethoxy-quinazolin-4-yl)-6,7-dimethyl-2,3-dihydro-1H-

indol-5-ol hydrochloride salt

Utilizing a procedure analogous to that described in Example 47 this product (with conversion to the HCl salt as outlined for Example 2) was prepared in 40% yield from 5-hydroxy-6,7-dimethyl-indoline (1.1 eq.), and 4-chloro-6,7-dimethoxy-quinazoline (1.0 eq) in N-methyl-pyrrolidinone. (M.P. 207-209° C (dec); LC-MS: 352 (MH⁺); anal. RP18-HPLC RT: 3.48 min.).

Example 574-(5,7-Dichloro-2,3-dihydro-indol-1-yl)-6,7-dimethoxy-quinazoline acetate salt

Utilizing a procedure analogous to that described in Example 47 this product was prepared in 16% yield from 5,7-dichloro-indoline (1.1 eq.), and 4-chloro-6,7-dimethoxy-quinazoline (1.0 eq) in N-methyl-pyrrolidinone. The product was isolated as its acetate salt by preparative RP(C18)-HPLC using a gradient of 10 to 60% CH₃CN/pH4.5, 50 mM NH₄OAc followed by lyophilization. (M.P. 228-232.5° C ; LC-MS: 376 (MH⁺); anal. RP18-HPLC RT: 5.20 min.).

Example 58

10 4-(6-Chloro-5-nitro-2,3-dihydro-indol-1-yl)-6,7-dimethoxy-quinazoline

Utilizing a procedure analogous to that described in Example 47 this product was prepared in 24% yield from 6-chloro-5-nitro-indoline (1.1 eq.), and 4-chloro-6,7-dimethoxy-quinazoline (1.0 eq) in N-methyl-pyrrolidinone. (M.P. 276-278° C ; LC-MS: 387 (MH⁺); anal. RP18-HPLC RT: 4.48 min.).

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Example 59

6-Chloro-1-(6,7-dimethoxy-quinazolin-4-yl)-2,3-dihydro-1H-indol-5-ylamine hydrochloride salt

To 4-(6-chloro-5-nitro-2,3-dihydro-indol-1-yl)-6,7-dimethoxy-quinazoline (150 mg, 0.386 mmol; from Example 58) in THF (5 mL) with 10% Pd-C (21 mg) at 40°C was added NaH₂PO₂·H₂O (490 mg, 3.86 mmol) in H₂O (0.5 mL) dropwise over 20 minutes. The mixture was stirred at 40°C for 5 hours. Following removal of the catalyst by filtration through Celite, and concentration in vacuo the residue was dissolved in 10% i-PrOH/CHCl₃, washed with saturated aqueous NaHCO₃, and brine, dried over Na₂SO₄, filtered and concentrated in vacuo to afford 121 mg (90%) of product which was converted to the HCl salt as outlined for Example 2. (M.P. 223-228° C ; LC-MS: 357 (MH⁺); anal. RP18-HPLC RT: 3.68 min.).

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Example 604-(4-Bromo-7-methyl-2,3-dihydro-indol-1-yl)-7-methoxy-quinazoline

Utilizing a procedure analogous to that described in Example 1, this product was prepared in 69% yield from 4-bromo-7-methyl-indoline (1.1 eq.), and 4-chloro-7-methoxy-quinazoline (1.0 eq) in i-PrOH. (M.P. 134-135° C ; LC-MS: 370, 372 (MH⁺); anal. RP18-HPLC RT: 5.60 min.).

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Example 614-(6-Bromo-7-methyl-2,3-dihydro-indol-1-yl)-7-methoxy-quinazoline hydrochloride salt

Utilizing a procedure analogous to that described in Example 1 (with conversion to the HCl salt as outlined for Example 2), this product was prepared in 49% yield from 6-bromo-7-methyl-indoline (1.1 eq.), and 4-chloro-7-methoxy-quinazoline (1.0 eq) in *i*-PrOH. (M.P. 200-205° C (dec); LC-MS: 370, 372 (MH⁺); anal. RP18-HPLC RT: 5.76 min.).

Example 627-Methoxy-4-(7-methyl-2,3-dihydro-indol-1-yl)-quinazoline

Utilizing a procedure analogous to that described in Example 1 this product was prepared in 79% yield from 7-methyl-indoline (1.1 eq.), and 4-chloro-7-methoxy-quinazoline (1.0 eq) in *i*-PrOH. (M.P. 157-160° C (dec); LC-MS: 292 (MH⁺); anal. RP18-HPLC RT: 4.30 min.).

Example 634-(6-Bromo-5-fluoro-2,3-dihydro-indol-1-yl)-7-methoxy-quinazoline hydrochloride salt

Utilizing a procedure analogous to that described in Example 1 (with conversion to the HCl salt as outlined for Example 2), this product was prepared in 74% yield from 6-bromo-5-fluoro-indoline (1.1 eq.), and 4-chloro-7-methoxy-quinazoline (1.0 eq) in *i*-PrOH. (M.P. 252-252° C ; LC-MS: 374, 376 (MH⁺); anal. RP18-HPLC RT: 5.26 min.).

Example 644-(6-Chloro-2,3-dihydro-indol-1-yl)-7-methoxy-quinazoline hydrochloride salt

Utilizing a procedure analogous to that described in Example 1 (with conversion to the HCl salt as outlined for Example 2), this product was prepared in 82% yield from 6-chloro-indoline (1.1 eq.), and 4-chloro-7-methoxy-quinazoline (1.0 eq) in *i*-PrOH. (M.P. of free-base: 140-141° C; For HCl salt: M.P. 232-233° C ; LC-MS: 312 (MH⁺); anal. RP18-HPLC RT: 5.68 min.).

Example 654-(6-Chloro-2,3-dihydro-indol-1-yl)-quinazolin-7-ol

4-(6-Chloro-2,3-dihydro-indol-1-yl)-7-methoxy-quinazoline (7.596 g, 24.4 mmol; free-base from Example 64) was added in several portions over 5 minutes to molten pyridine hydrochloride (85g) at 170°C. The stoppered mixture was heated 75 minutes and then poured into ice/water (~ 600 mL). The precipitated solid was

filtered, dissolved in 10% i-PrOH/CHCl₃, and the organic solution was washed with saturated aqueous NaHCO₃ and brine, dried over Na₂SO_{4(s)}, filtered and concentrated in vacuo to afford 3.14 g. of product. (M.P. 270-280° C (dec); LC-MS: 298 (MH⁺); anal. RP18-HPLC RT: 4.00 min.).

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Example 66

4-(6-Chloro-2,3-dihydro-indol-1-yl)-7-(2-methoxy-ethoxy)-
quinazoline hydrochloride salt

To 4-(6-chloro-2,3-dihydro-indol-1-yl)-quinazolin-7-ol (125 mg, 0.42 mmol; from Example 65) in DMF (2 mL) was added H₂O (50 µL), K₂CO_{3(s)} (116 mg, 0.84 mmol), and tetramethylammonium hydroxide pentahydrate (15 mg, 0.08 mmol) followed by 2-bromoethyl methyl ether (43 µL, 0.46 mmol). The mixture was stirred at 50°C under N_{2(g)} for 24 hours before another aliquot (43 µL) of 2-bromoethyl methyl ether was added. Stirring at 50°C was continued for another 36 hours before extractive workup and chromatography analogous to that described in Example 1 followed by conversion to the HCl salt as outlined for Example 2 afforded 91 mg (61%) of product. (M.P. 213-216° C (dec); LC-MS: 356 (MH⁺); anal. RP18-HPLC RT: 4.73 min.).

Example 67

2-[4-(6-Chloro-2,3-dihydro-indol-1-yl)-quinazolin-7-yloxy]-ethanol hydrochloride salt

To 4-(6-chloro-2,3-dihydro-indol-1-yl)-quinazolin-7-ol (125 mg, 0.42 mmol; from Example 65) in DMF (2 mL) was added H₂O (50 µL), K₂CO_{3(s)} (116 mg, 0.84 mmol), and tetramethylammonium hydroxide pentahydrate (15 mg, 0.08 mmol) followed by 2-bromoethanol (39 µL, 0.46 mmol). The mixture was stirred at 50°C under N_{2(g)} and aliquots of 2-bromoethanol (3 X 20 µL) were added at 24 hour intervals. Extractive workup and chromatography analogous to that described in Example 1 followed by conversion to the HCl salt as outlined for Example 2 afforded 76 mg (53%) of product. (M.P. 215-217° C ; LC-MS: 342 (MH⁺); anal. RP18-HPLC RT: 4.09 min.).

Example 68

3-[4-(6-Chloro-2,3-dihydro-indol-1-yl)-quinazolin-7-yloxy]-
propan-1-ol hydrochloride salt

To 4-(6-chloro-2,3-dihydro-indol-1-yl)-quinazolin-7-ol (125 mg, 0.42 mmol; from Example 65) in DMF (2 mL) was added H₂O (50 µL), K₂CO_{3(s)} (116 mg, 0.84

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mmol) and tetramethylammonium hydroxide pentahydrate (15 mg, 0.08 mmol) followed by 3-bromopropanol (43 μ L, 0.46 mmol). The mixture was stirred at 50°C under N_{2(g)} for 24 hours before another aliquot (11 μ L) of 3-bromopropanol was added. After heating another 24 hours, extractive workup and chromatography
5 analogous to that described in Example 1 followed by conversion to the HCl salt as outlined for Example 2 afforded 119 mg (70%) of product. (M.P. 211-223°C (dec); LC-MS: 356 (MH⁺); anal. RP18-HPLC RT: 4.40 min.; M.P. of free-base: 137-138°C).

Examples 69 & 70

4-(6-Chloro-2,3-dihydro-indol-1-yl)-quinazoline-6,7-diol

10

and

4-(6-Chloro-2,3-dihydro-indol-1-yl)-6-methoxy-quinazolin-7-ol

4-(6-Chloro-2,3-dihydro-indol-1-yl)-6,7-dimethoxy-quinazoline (1.00 g, 2.93 mmol; from Example 3) was added to molten pyridinium hydrochloride (10.14 g, 88 mmol) at 170°C. The mixture was stirred at 170°C for 0.5-1.0 hours (until <5%
15 starting material remained by anal.RP-HPLC), and then poured into ice/water (110 mL). The precipitated orange solid was recovered by filtration, dried by azeotropic removal of H₂O with CH₃CN at 40°C in vacuo, dissolved in 15% i-PrOH/CHCl₃ (75 mL) and washed with saturated aqueous NaHCO₃ (2X). The organic phase was dried over Na₂SO_{4(s)}, filtered and concentrated in vacuo. The residue (~ 800 mg)
20 was triturated with CHCl₃ (60 mL) and filtered to recover the 6,7-diol (typically 200 mg, 94% purity; used without further purification)(M.P. 200° C (dec); LC-MS: 314 (MH⁺); anal. RP18-HPLC RT: 4.07 min.). The filtrate was flash chromatographed on silica (40 to 80% acetone/CH₂Cl₂) to afford ~ 550 mg of the pure 6-methoxy-quinazolin-7-ol product (M.P. 175° C (dec); LC-MS: 328 (MH⁺); anal. RP18-HPLC
25 RT: 4.07 min.).

Example 71

4-(6-Chloro-2,3-dihydro-indol-1-yl)-6-methoxy-7-(2-methoxy-ethoxy)-quinazoline methanesulfonate salt

4-(6-Chloro-2,3-dihydro-indol-1-yl)-6-methoxy-quinazolin-7-ol (100 mg, 0.305
30 mmol; from Example 70) was reacted with 2-bromoethyl methyl ether as described in Example 66 and worked-up as described for Example 1 to yield 53 mg of product which was converted to the methanesulfonate salt as outlined in Example 44. (M.P. 248° C (dec); LC-MS: 386 (MH⁺); anal. RP18-HPLC RT: 4.56 min.).

Example 724-(6-Chloro-2,3-dihydro-indol-1-yl)-6,7-bis-(2-methoxy-ethoxy)-quinazoline
methanesulfonate salt

To 4-(6-chloro-2,3-dihydro-indol-1-yl)-quinazoline-6,7-diol (250 mg, 0.797
5 mmol; from Example 69) dissolved in DMF (4 mL) was added H₂O (50 μ L), K₂CO₃(s)
(330 mg, 2.39 mmol), and tetramethylammonium hydroxide pentahydrate (15 mg,
0.08 mmol) followed by 2-bromoethyl methyl ether (225 μ L, 2.39 mmol). The mixture
was stirred at 50°C under N_{2(g)} for 5 hours and then worked-up as described for
Example 1 to yield 131 mg of product which was converted to the methanesulfonate
10 salt as outlined in Example 44. (M.P. 185° C (dec); LC-MS: 430 (MH⁺); anal. RP18-
HPLC RT: 4.68 min.).

Examples 73 & 74[4-(6-Chloro-2,3-dihydro-indol-1-yl)-6-methoxy-quinazolin-
7-yloxy]-acetic acid ethyl ester

15 and
[4-(6-Chloro-2,3-dihydro-indol-1-yl)-6-methoxy-quinazolin-7-yloxy]-acetic acid lithium
salt

To 4-(6-chloro-2,3-dihydro-indol-1-yl)-6-methoxy-quinazolin-7-ol (128 mg,
0.333 mmol; from Example 70) in DMF (2 mL) was added potassium tert-butoxide
20 (0.381 mL of 1.0M in THF) followed within minutes by ethyl 2-bromoacetate (47 μ L,
0.420 mmol). The mixture was stirred for 16 hours at 20°C, and then partitioned
between CHCl₃ and 5% aqueous NaHCO₃. The organic phase was washed with
brine, dried over Na₂SO_{4(s)}, filtered and concentrated in vacuo. The residue was
recrystallized from CHCl₃/ hexane to afford 30 mg of the ester as a pale yellow solid.
25 (M.P. 175-176° C; GC-MS: 413 (M⁺); anal. RP18-HPLC RT: 5.34 min.).

The filtrate from the recrystallization was dissolved in MeOH (6mL) and H₂O
(3 mL) and LiOH (30 mg, 0.666 mmol) was added. The mixture was heated to reflux
for 1 hour, and the volume was reduced ~65% in vacuo before washing the
aqueous phase with Et₂O. The pH of the aqueous phase was adjusted to 3.5 using
30 AcOH and the mixture was chilled to 4°C to precipitate the free-acid product (73
mg), which was converted to its lithium salt by treatment with 1.00eq. of LiOH in
MeOH and precipitation on dilution with Et₂O. (M.P. 240-255° C (dec); NEG-FAB:
390 (M-H⁻); anal. RP18-HPLC RT: 3.00 min.).

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Example 752-[4-(6-Chloro-2,3-dihydro-indol-1-yl)-6-methoxy-quinazolin-7-yloxy]-ethanolmethanesulfonate salt

To 4-(6-chloro-2,3-dihydro-indol-1-yl)-6-methoxy-quinazolin-7-ol (271 mg, 0.828 mmol; from Example 70) in DMF (3 mL) was added tetramethylammonium hydroxide pentahydrate (75 mg, 0.305 mmol), K_2CO_3 (171 mg, 1.24 mmol) and H_2O (50 μ L) followed by 2-bromoethanol (79 μ L, 1.11 mmol). The mixture was stirred at 50°C and further additions of 2-bromoethanol (1.0 eq.) were made daily. After 4 days the mixture was partitioned between $CHCl_3$ and brine. The organic phase was washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4 , filtered and concentrated in vacuo. Flash chromatography (40% acetone/ CH_2Cl_2) of the residue on silica yielded 269 mg (87%) of the free-base (M.P. 205-206°C) which was converted to a hydrochloride salt according to the analogous method in Example 2 (M.P. 190-204°C (dec).), or a methanesulfonate salt by the analogous method in Example 44. (M.P. 233-237°C (dec); LC-MS: 372 (MH^+); anal. RP18-HPLC RT: 3.90 min.).

Example 764-(6-Chloro-2,3-dihydro-indol-1-yl)-6-methoxy-7-(2-morpholin-4-yl-ethoxy)-quinazolinebis(methanesulfonate) salt

To a stirred solution of 4-(6-chloro-2,3-dihydro-indol-1-yl)-6-methoxy-quinazolin-7-ol (200 mg, 0.610 mmol; from Example 70) and triphenylphosphine (160 mg, 0.610 mmol) in dry THF (3 mL) under $N_{2(g)}$ was added diethyl-azodicarboxylate (106 μ L, 0.671 mmol) dropwise at 0°C over 10 minutes followed by a solution of 4-(2-hydroxyethyl)-morpholine (81 μ L, 0.671 mmol) in dry THF (0.8 mL). The mixture was allowed to warm to 20°C and stirred 16 hours before quenching with H_2O (20 μ L) and concentrating in vacuo. Flash chromatography of the residue on silica using first 45% acetone/ CH_2Cl_2 followed by 10% MeOH/ CH_2Cl_2 eluted the product as its free-base (180 mg), which was precipitated as its bis(methanesulfonate) salt by addition of 2.0 eq. of methanesulfonic acid to a solution in CH_2Cl_2 . (M.P. 150-158°C (dec); LC-MS: 441 (MH^+); anal. RP18-HPLC RT: 3.76 min.).

Example 774-(6-Chloro-2,3-dihydro-indol-1-yl)-7-(2-imidazol-1-yl-ethoxy)-6-methoxy-quinazoline
bis(methanesulfonate) salt

This product was produced in 50% yield from 4-(6-chloro-2,3-dihydro-indol-1-yl)-6-methoxy-quinazolin-7-ol and N-(2-hydroxyethyl)imidazole (1.1 eq.) in a manner analogous to that described for Example 76. (M.P. 162-168° C (dec); LC-MS: 422 (MH⁺); anal. RP18-HPLC RT: 3.94 min.).

Example 781-[4-(6-Chloro-2,3-dihydro-indol-1-yl)-6-methoxy-quinazolin-7-yloxy]-3-methoxy-
propan-2-ol methanesulfonate salt

To 4-(6-chloro-2,3-dihydro-indol-1-yl)-6-methoxy-quinazolin-7-ol (125 mg, 0.381 mmol; from Example 70) in DMF (2 mL) was added tetramethylammonium hydroxide pentahydrate (15 mg, 0.076 mmol), K₂CO_{3(s)} (79 mg, 0.572 mmol) and H₂O (50 µL) followed by methyl glycidyl ether (37 µL, 0.42 mmol). The mixture was stirred at 50°C and further additions of methyl glycidyl ether (0.5 eq.) were made daily. After 4 days the mixture was partitioned between CHCl₃ and brine. The organic phase was washed with saturated aqueous NaHCO₃ and brine, dried over Na₂SO_{4(s)}, filtered and concentrated in vacuo. Flash chromatography (25->40% acetone/CH₂Cl₂) of the residue on silica yielded 56% of the free-base (M.P. 89-90°C) which was converted to the methanesulfonate salt as outlined in Example 44. (M.P. 180-187° C (dec); LC-MS: 416 (MH⁺); anal. RP18-HPLC RT: 3.81 min.).

Example 792-[4-(6-Chloro-2,3-dihydro-indol-1-yl)-6-methoxy-quinazolin-7-yloxy]-propanol
methanesulfonate salt

To 4-(6-chloro-2,3-dihydro-indol-1-yl)-6-methoxy-quinazolin-7-ol (328 mg, 1.0 mmol; from Example 70) in DMF (2 mL) was added tetramethylammonium hydroxide pentahydrate (27 mg, 0.2 mmol), K₂CO_{3(s)} (276 mg, 2.0 mmol) and H₂O (50 µL) followed by 3-bromopropanol (90 µL, 1.0 mmol). The mixture was stirred at 50°C for 16 hours. Following extractive work-up, chromatography on silica (55% acetone/hexanes)(M.P. of free-base: 152-153°C), and salt formation analogous to that described for Example 78 the product was obtained in 84% yield. (M.P. 195-205° C (dec); LC-MS: 386 (MH⁺); anal. RP18-HPLC RT: 3.95 min.).

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Example 80[4-(6-Chloro-2,3-dihydro-indol-1-yl)-7,8-dihydro-[1,4]dioxino[2,3-g]
quinazolin-7-yl]-methanol

To 4-(6-chloro-2,3-dihydro-indol-1-yl)-quinazoline-6,7-diol (99 mg, 0.316
5 mmol; from Example 69) dissolved in DMF (2 mL) was added H₂O (100 μ L),
K₂CO₃(s) (65 mg, 0.473 mmol), and tetramethylammonium hydroxide pentahydrate
(11 mg, 0.06 mmol) followed by epibromohydrin (28 μ L, 0.331 mmol). The mixture
was stirred at 50°C under N_{2(g)} for 16 hours. Following extractive work-up, and
chromatography on silica (20% acetone/CH₂Cl₂) analogous to that described for
10 Example 78 the product was obtained in 11% yield. (M.P. 219-222° C (dec); LC-
MS: 370 (MH⁺); anal. RP18-HPLC RT: 3.98 min.).

Example 814-(6-Bromo-5-fluoro-2,3-dihydro-indol-1-yl)-6,7-bis-(2-methoxy-ethoxy)-quinazoline
hydrochloride salt

15 Utilizing a procedure analogous to that described in Example 1, this product
was prepared in 78% yield from 6-bromo-5-fluoro-indoline (1.1 eq.), and 4-chloro-6,7-
bis-(2-methoxy-ethoxy)-quinazoline (1.0 eq) in i-PrOH. (M.P. of free-base: 146-
148°C)(For HCl salt: M.P. 215-223° C (dec); LC-MS: 492, 494 (MH⁺); anal. RP18-
HPLC RT: 4.64 min.).

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Example 824-(6-Bromo-5-fluoro-2,3-dihydro-indol-1-yl)-6-methoxy-7-(2-methoxy-ethoxy)-
quinazoline hydrochloride salt

Utilizing a procedure analogous to that described in Example 1, this product
was prepared in 58% yield from 6-bromo-5-fluoro-indoline (1.1 eq.), and 4-chloro-6-
25 methoxy-7-(2-methoxy-ethoxy)-quinazoline (1.0 eq) in i-PrOH. (M.P. of free-base:
150-150.5°C)(For HCl salt: M.P. 243-251° C (dec); LC-MS: 448, 450 (MH⁺); anal.
RP18-HPLC RT: 4.79 min.).

Example 831-(6,7-Dimethoxy-quinazolin-4-yl)-2,3-dihydro-1H-indol-5-ylamine hydrochloride salt

30 The (5-nitro-indolin-1-yl)-6,7-dimethoxy-quinazoline (412 mg, 1.17 mmol)
produced in Example 52 was hydrogenated under 50 psi of H₂(g) in MeOH (10
mL)/HOAc (20 mL) with 11.7 M HCl (2 mL) in the presence of 10% Pd-C (200 mg)
for 24 hours. Following workup analogous to that described in Example 30 and

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chromatography on silica (5% MeOH/ CH₂Cl₂) gave the product (91%, 372 mg) which was converted to the HCl salt analogous to that in Example 2. (M.P. 277-280° C (dec); LC-MS: 323 (MH⁺); anal. RP18-HPLC RT: 2.74 min.).

Example 84

5 1-(6,7-Dimethoxy-quinazolin-4-yl)-2,3-dihydro-1H-indole-2-carboxylic acid lithium salt

To 1-(6,7-dimethoxy-quinazolin-4-yl)-2,3-dihydro-1H-indole-2-carboxylic acid methyl ester (500 mg, 1.37 mmol; from Example 24) in MeOH (8 mL)/H₂O (4 mL) was added LiOH (56 mg, 1.37 mmol). The solution was heated briefly to reflux (~5 minutes) and cooled to 20°C and concentrated in vacuo to afford the lithium salt of
10 the acid. (FAB-MS: 352 (MH⁺), 358 (M-H+Li)⁺; anal. RP18-HPLC RT: 2.53 min.).

Example 85

N-[1-(6,7-Dimethoxy-quinazolin-4-yl)-2,3-dihydro-1H-indol-6-yl]-acetamide

To 1-(6,7-dimethoxy-quinazolin-4-yl)-2,3-dihydro-1H-indol-6-ylamine (99 mg, 0.307 mmol; from Example 30) and pyridine (32 μL, 0.620 mmol) in CHCl₃ (5 mL) was
15 added acetyl chloride (33 μL, 0.455 mmol). The mixture was refluxed 2 hours, diluted with CHCl₃ (15 mL), and the organic solution was washed with saturated aqueous NaHCO₃, dried over Na₂SO_{4(a)}, filtered and concentrated in vacuo. Flash chromatography on silica (5% MeOH/CHCl₃) afforded 77 mg of product. (M.P. 223-229° C (dec); GC-MS: 364 (M⁺); anal. RP18-HPLC RT: 3.42 min.).

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Example 86

N-[1-(6,7-Dimethoxy-quinazolin-4-yl)-2,3-dihydro-1H-indol-6-yl]-

2,2,2-trifluoro-acetamide

To 1-(6,7-dimethoxy-quinazolin-4-yl)-2,3-dihydro-1H-indol-6-ylamine (119 mg, 0.369 mmol; from Example 30) and pyridine (42 μL, 0.79 mmol) in CH₂Cl₂ (5 mL) was
25 added trifluoroacetic anhydride (112 μL, 0.79 mmol). The mixture was stirred at 20°C for 6 hours, quenched with H₂O (5 mL), stirred 30 minutes and diluted with CHCl₃ (15 mL). The organic phase was separated and washed with saturated aqueous NaHCO₃, dried over Na₂SO_{4(a)}, filtered and concentrated in vacuo. Flash chromatography on silica (3% MeOH/CHCl₃) afforded 109 mg of product. (M.P.
30 240° C (dec); GC-MS: 418 (M⁺); anal. RP18-HPLC RT: 4.20 min.).

Example 87N-[1-(6,7-Dimethoxy-quinazolin-4-yl)-2,3-dihydro-1H-indol-5-yl]-acetamide

To 1-(6,7-dimethoxy-quinazolin-4-yl)-2,3-dihydro-1H-indol-5-ylamine (102 mg, 0.316 mmol; free-base from Example 83) and 4-(N,N-dimethylamino)pyridine (51.2 mg, 0.42 mmol) in CH₂Cl₂ (5 mL) was added acetic anhydride (88 μ L, 0.93 mmol).
5 The mixture was stirred at 20°C for 7.5 hours, quenched with H₂O (5 mL), stirred 30 min. and diluted with CHCl₃ (15 mL). The organic phase was separated and washed with saturated aqueous NaHCO₃, dried over Na₂SO_{4(s)}, filtered and concentrated in vacuo. Flash chromatography on silica (3.5% MeOH/CHCl₃) afforded 53 mg of
10 product. (M.P. >250° C (dec); LC-MS: 365 (MH⁺); anal. RP18-HPLC RT: 2.79 min.).

Example 88N-[1-(6,7-Dimethoxy-quinazolin-4-yl)-2,3-dihydro-1H-indol-5-yl]-formamide

Formic acid (42 μ L) was added to acetic anhydride (88 μ L) while stirring at 5°C and the mixture was allowed to stir at 20°C for 1 hour before adding 1-(6,7-dimethoxy-quinazolin-4-yl)-2,3-dihydro-1H-indol-5-ylamine (102 mg, 0.316 mmol; free-base from Example 83). The mixture was stirred at 20°C for 1.5 hours, quenched with H₂O (5 mL), stirred 30 min. and diluted with CHCl₃ (15 mL). The organic phase was separated and washed with saturated aqueous NaHCO₃, dried over Na₂SO_{4(s)}, filtered and concentrated in vacuo. Flash chromatography on silica (4%
15 MeOH/CH₂Cl₂) afforded 66 mg of product. (M.P. 239-244° C (dec); LC-MS: 351 (MH⁺); anal. RP18-HPLC RT: 2.92 min.).
20

Example 898-Bromo-1-(6,7-dimethoxy-quinazolin-4-yl)-2,3,4,5-tetrahydro-1H-benzo[b]azepine

Utilizing a procedure analogous to that described in Example 47, this product
25 was prepared in 58% yield from 8-bromo-2,3,4,5-tetrahydro-1H-benzo[b]azepine (1.1 eq.), and 4-chloro-6,7-dimethoxy-quinazoline (1.0 eq) in N-methyl-pyrrolidinone. (M.P. 209-217° C ; LC-MS: 414, 416 (MH⁺); anal. RP18-HPLC RT: 5.47 min.).

Example 901-(6,7-Dimethoxy-quinazolin-4-yl)-1,2,3,4,5,6-hexahydro-benzo[b]azocine

Utilizing a procedure analogous to that described in Example 47, this product
30 was prepared in 67% yield from 1,2,3,4,5,6-hexahydro-benzo[b]azocine (1.1 eq.), and 4-chloro-6,7-dimethoxy-quinazoline (1.0 eq) in N-methyl-pyrrolidinone. (M.P. 204-207° C ; GC-MS: 349 (M⁺); anal. RP18-HPLC RT: 5.25 min.).

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Example 914-(6-Chloro-2,3-dihydro-indol-1-yl)-6-methoxy-quinazoline

Utilizing a procedure analogous to that described in Example 1, this product was prepared in 77% yield from 6-chloro-indoline and 4-chloro-6-methoxy-quinazoline. (M.P.

5 243 °C; LC-MS: 312 (MH⁺)).

Example 924-(3,4-Dihydro-2H-quinolin-1-yl)-7-methoxy-6-methylsulfanyl-quinazoline

Utilizing a procedure analogous to that described in Example 1, this product was prepared in 35% yield from 1,2,3,4-tetrahydroquinoline and 4-chloro-7-methoxy-6-

10 methylsulfanyl-quinazoline. (M.P. 193-196 °C; LC-MS: 338 (MH⁺)).

Example 934-(6-Chloro-2,3-dihydro-indol-1-yl)-6-methyl-quinazoline

Utilizing a procedure analogous to that described in Example 24, this product was prepared in 15% yield from 6-chloro-indoline and 4-chloro-6-methyl-quinazoline.

15 (M.P. 138-41°C; LC-MS: 296 (MH⁺)).

Example 944-(6-Chloro-2,3-dihydro-indol-1-yl)-7-methoxy-6-methylsulfanyl-quinazoline

Utilizing a procedure analogous to that described in Example 1, this product was prepared in 18% yield from 6-chloro-indoline and 4-chloro-7-methoxy-6-methylsulfanyl-

20 quinazoline. (M.P. 210 °C; LC-MS: 358 (MH⁺)).

Example 954-(6-Chloro-2,3-dihydro-indol-1-yl)-6,7-dimethyl-quinazoline

Utilizing a procedure analogous to that described in Example 24, this product was prepared in 16% yield from 6-chloro-indoline and 4-chloro-6,7-dimethyl-quinazoline.

25 (M.P. 199 °C; LC-MS: 310 (MH⁺)).

Example 967-Chloro-4-(6-chloro-2,3-dihydro-indol-1-yl)-6-(2-methoxy-ethylsulfanyl)-quinazoline

Utilizing a procedure analogous to that described in Example 1, this product was prepared in 38% yield from 6-chloro-indoline and 4,7-dichloro-6-(2-methoxy-

30 ethylsulfanyl)quinazoline. (M.P. 104-106 °C; LC-MS: 406 (MH⁺)).

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Example 977-Chloro-4-(6-chloro-2,3-dihydro-indol-1-yl)-quinazoline

Utilizing a procedure analogous to that described in Example 24, this product was prepared in 50% yield from 6-chloro-indoline and 4,7-dichloro-quinazoline. (M.P. 189 °C; LC-MS: 316 (MH⁺)).

Example 988-Chloro-4-(6-chloro-2,3-dihydro-indol-1-yl)-quinazoline

Utilizing a procedure analogous to that described in Example 24, this product was prepared in 47% yield from 6-chloro-indoline and 4,8-dichloro-quinazoline. (M.P. 190 °C; LC-MS: 316 (MH⁺)).

Example 99(6-Chloro-4-(6-chloro-2,3-dihydro-indol-1-yl)-7-methoxy-quinazoline

Utilizing a procedure analogous to that described in Example 1, this product was prepared in 17% yield from 6-chloro-indoline and 4,6-dichloro-7-methoxy-quinazoline. (M.P. 226 °C; LC-MS: 346 (MH⁺)).

Example 100(7-Chloro-4-(6-chloro-2,3-dihydro-indol-1-yl)-6-methylsulfanyl-quinazoline

Utilizing a procedure analogous to that described in Example 1, this product was prepared in 15% yield from 6-chloro-indoline and 4,7-dichloro-6-methylsulfanyl-quinazoline. (M.P. 167-168 °C; LC-MS: 362 (MH⁺)).

Example 101(4-(6-Chloro-2,3-dihydro-indol-1-yl)-7-methyl-quinazoline

Utilizing a procedure analogous to that described in Example 24, this product was prepared in 14% yield from 6-chloro-indoline and 4-chloro-7-methyl-quinazoline. (M.P. 265°C; LC-MS: 296 (MH⁺)).

Example 102(4-(5-Bromo-3,4-dihydro-2H-quinolin-1-yl)-6,7-dimethoxy-quinazoline

Utilizing a procedure analogous to that described in Example 1, this product was prepared in 4% yield from 5-bromo-1,2,3,4-tetrahydroquinoline and 4-chloro-6,7-dimethoxy-quinazoline. (film; LC-MS: 399 (MH⁺)).

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Example 1034-(7-Bromo-3,4-dihydro-2H-quinolin-1-yl)-6,7-dimethoxy-quinazoline

Utilizing a procedure analogous to that described in Example 1, this product was prepared in 11% yield from 7-bromo-1,2,3,4-tetrahydroquinoline and 4-chloro-6,7-dimethoxy-quinazoline. (film; LC-MS: 399 (MH⁺)).

Example 104[(4-(3,4-Dihydro-2H-quinolin-1-yl)-6-methoxy-quinazolin-7-yloxy)-acetic acid ethyl ester]

Utilizing a procedure analogous to that described in Example 1, this product was prepared in 2% yield from 1,2,3,4-tetrahydroquinoline and (4-chloro-6-methoxy-quinazolin-7-yloxy)-acetic acid ethyl ester. (film; LC-MS: 393 (MH⁺)).

Example 105[(4-(3,4-Dihydro-2H-quinolin-1-yl)-7-ethoxycarbonylmethoxy-quinazolin-6-yloxy)-acetic acid ethyl ester]

Utilizing a procedure analogous to that described in Example 1, this product was prepared in 19% yield from 1,2,3,4-tetrahydroquinoline and (4-chloro-7-ethoxycarbonylmethoxy-quinazolin-6-yloxy)-acetic acid ethyl ester. (film; LC-MS: 465 (MH⁺)).

Example 1064-(6-Chloro-2,3-dihydro-indol-1-yl)-7-nitro-quinazoline hydrochloride

4-Chloro-7-nitroquinazoline (11.22g, 53.5 mmol) was slurried into 35 ml isopropanol, treated with 6-chloroindoline (8.25g, 53.7 mmol), refluxed for three hours, then cooled slowly to room temperature. Product was filtered and air dried overnight to afford bright yellow powder; 13.18 g (68%); M.P. 230°C (dec); LC-MS: 327 (MH⁺), 329 ((M+2)H⁺); Calc. C₁₆H₁₁ClN₄O₂·HCl: C,52.91; H,3.3; N,15.43; Cl,19.52; Found: C,52.77; H,3.61; N,14.78; Cl,19.62.

Example 1074-(6-Chloro-2,3-dihydro-indol-1-yl)-quinazolin-7-yl amine hydrochloride

4-(6-Chloro-2,3-dihydro-indol-1-yl)-7-nitro-quinazoline hydrochloride (2.16 g, 5.90 mmol) was slurried in 250 mL of ethanol containing 0.21 g of 10% palladium on carbon and treated with ammonium formate (1.68 g, 26.6 mmol). After 16 hours the mixture was filtered through celite and evaporated in vacuo to a residue. This was dissolved in chloroform, filtered and washed with sodium bicarbonate and brine then

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dried with magnesium sulfate, filtered and evaporated in vacuo to give crude product which was recrystallized from 50% aqueous ethanol. The solid was dissolved in methanol containing anhydrous hydrogen chloride and poured into ether to yield the title compound after filtration and drying in vacuo; 0.687 g (35%)
5 M.P. 282-283°C.

Example 108

N-[4-(6-Chloro-2,3-dihydro-indol-1-yl)-quinazolin-7-yl] methanesulfonamide

4-(6-Chloro-2,3-dihydro-indol-1-yl)-quinazolin-7-yl amine hydrochloride (0.155 g, 0.465 mmol) was reacted with methanesulfonyl chloride (0.0531, 0.465 mmol) and
10 triethylamine (0.290 g, 2.87 mmol) in 5 mL of chloroform at 0 °C for one hour and 16 hours at room temperature. The reaction mixture was poured into 50 mL of water and extracted with 3 x 50 mL of ethyl acetate. The pooled organic layers were washed with 50 mL of brine, dried with magnesium sulfate, filtered and vacuum
15 evaporated to a yellow residue, 0.121 g. This was purified by chromatography using a Chromatotron mounted with a 2 mm silica gel plate and eluted with 5% methanol in chloroform. Pure product was isolated by vacuum evaporation of the appropriate fractions; 0.015 g (8.7%) M.P. 240-245 °C (dec) .

Example 109

N-[4-(6-Chloro-2,3-dihydro-indol-1-yl)-quinazolin-7-yl]

bismethanesulfonamide

4-(6-Chloro-2,3-dihydro-indol-1-yl)-quinazolin-6-yl-amine hydrochloride (0.1495 g, 0.449 mmol) was slurried into 5 mL methylene chloride. Triethylamine (1.2 mL, 8.6 mmol) was added and the reaction was cooled to 0°C. Methanesulfonyl chloride (0.105 mL, 1.36 mmol) was added and the reaction warmed to room temperature.
25 After 30 minutes, the mixture was poured into 20 mL water, extracted with methylene chloride (3 X 20 mL), washed with saturated aqueous sodium bicarbonate and with brine, dried over magnesium sulfate, filtered, and solvent removed in vacuo to afford yellow foam, 0.177g (87%); LC-MS: 453 (MH⁺), 455 ((M+2)H⁺).

Example 110

N-[4-(6-Chloro-2,3-dihydro-indol-1-yl)-quinazolin-7-yl]-hydroxylamine

4-(6-Chloro-2,3-dihydro-indol-1-yl)-7-nitro-quinazoline hydrochloride (2.90g, 7.98 mmol) was dissolved in 700 mL methanol and hydrogenated with 10% palladium on carbon (0.50g) for 10 minutes at 3 atm. Reaction mixture was filtered

through celite and diluted with 1.5 L diethyl ether. Product was filtered and dried under vacuum to give bright yellow solid, 2.23 g (80%): M.P. 262-263°C (dec); GC-MS: 313 (M^+), 315 ($M^+ + 2$); Calc. $C_{16}H_{13}ClN_4O \cdot HCl$: C, 55.03; H, 4.04; N, 16.04; Found: C, 55.18; H, 4.28; N, 16.13.

5

Example 111[4-(6-Chloro-2,3-dihydro-indol-1-yl)-quinazolin-7-yl]-methylamine hydrochloride

4-(6-Chloro-2,3-dihydro-indol-1-yl)-quinazolin-7-ylamine hydrochloride (0.104 g, 0.313 mmol) was dissolved in 3 mL acetonitrile and treated with 0.141 mL 37% aqueous formaldehyde (1.74 mmol). Sodium cyanoborohydride (0.036 g, 0.571 mmol) was added slowly, then 0.05 mL acetic acid was added and the reaction was stirred at room temperature for two hours. Additional formaldehyde (1.74 mmol) and sodium cyanoborohydride (0.571 mmol) were added after thirty minutes, additional acetic acid (0.05 mL) was added at thirty minutes and at one hour. After two hours, the reaction mixture was poured into 50 mL diethyl ether and washed with 1N sodium hydroxide (3 X 50 mL), dried over magnesium sulfate, filtered and solvent removed in vacuo to give 0.913 yellow solid containing cyanohydroboramine derivatives of both monomethylated and dimethylated material.

Automated rotary thin-layer chromatography (Chromatotron®) using a 2 mm silica gel plate and eluting with chloroform, then 10% methanol in chloroform gave 0.0156 g of the cyanohydroboramine derivative of the monomethylated material, which was dissolved in 1 mL ethanol and treated with 0.8 mL 1N HCl in methanol and refluxed overnight. The resulting mixture was poured into 100 mL 1N sodium hydroxide, extracted with chloroform (4 X 50 mL), dried over magnesium sulfate, filtered and solvent removed in vacuo. Resulting yellow residue was dissolved in minimal methanol, treated with 1N HCl in methanol, precipitated by dilution with diethyl ether, filtered and dried in vacuo to give bright yellow solid, 0.010 g (9%): M.P. 270-274°C (dec); LC-MS: 311 (MH^+), 313 ($(M+2)H^+$).

Example 112[4-(6-Chloro-2,3-dihydro-indol-1-yl)-quinazolin-7-yl]-dimethylamine hydrochloride

Cyanohydroboramine derivative of the dimethylated material isolated by Chromatotron chromatography in Example 111 was treated in an identical manner with ethanolic HCl to give bright yellow solid, 0.0145g (13%): M.P. 281-282°C (dec); LC-MS: 325 (MH^+), 327 ($(M+2)H^+$).

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Example 1134-(6-Chloro-2,3-dihydro-indol-1-yl)-6-nitro-quinazoline

4-Chloro-6-nitroquinazoline (16.72 g, 79.8 mmol) was slurried into 250 ml isopropanol, treated with 6-chloroindoline (12.25 g, 79.8 mmol), refluxed for three hours, then cooled slowly to room temperature. Product was filtered and air dried overnight to afford 12.30 g of a bright yellow powder. This was heated at reflux in 100 mL of chloroform containing 15 mL of triethylamine for one hour. The cool suspension was filtered to afford pure title compound; 5.17 g (20%); M.P. 260-261°C (dec).

10

Example 114N-[4-(6-Chloro-2,3-dihydro-indol-1-yl)-quinazolin-6-yl]-formamide

4-(6-Chloro-2,3-dihydro-indol-1-yl)-7-nitro-quinazoline (5.17g, 15.8 mmol) was dissolved in 60 mL 96% formic acid. Sodium dithionite (13.78g, 79.2 mmol) was added slowly, ice bath was used to control reaction temperature. After 30 minutes, about half of the formic acid was removed in vacuo, and the remaining reaction mixture was poured into water and chloroform and basified to pH 13 with 6N NaOH, extracted with chloroform (3 X 100 mL), washed with brine (100 mL), dried over magnesium sulfate, filtered and solvent removed in vacuo to give bright yellow foam, 2.71 g (53%); LC-MS: 325 (MH⁺), 327 ((M+2)H⁺).

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Example 1154-(6-Chloro-2,3-dihydro-indol-1-yl)-quinazolin-6-ylamine hydrochloride

N-[4-(6-Chloro-2,3-dihydro-indol-1-yl)-quinazolin-6-yl]-formamide (1.0055 g, 3.10 mmol) was slurried into 20 mL methanol, treated with 20 mL 1N HCl in methanol, and stirred at room temperature for one hour. Dilution to 125 mL with diethyl ether afforded yellow solid, 0.8430 g (82%; another .089 g obtained from subsequent cooling of mother liquor); M.P. 289-290°C (dec); LC-MS: 297 (MH⁺), 299 ((M+2)H⁺).

25

Example 1164-(6-Chloro-2,3-dihydro-indol-1-yl)-quinazolin-6-yl]-methylamine

N-[4-(6-Chloro-2,3-dihydro-indol-1-yl)-quinazolin-6-yl]-formamide (.5010g, 1.54 mmol) in 6 mL tetrahydrofuran was added to a slurry of lithium aluminum hydride (0.1726 g, 4.55 mmol) in 5 mL tetrahydrofuran dropwise over 10 minutes. The reaction was stirred at room temperature for 15 minutes, then quenched by

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successive addition of 0.2 mL water, 0.2 mL 1N sodium hydroxide (aq) and 0.6 mL water, then was filtered and the filter cake washed thoroughly with water and ethyl acetate. The filtrate was extracted with ethyl acetate (3 X 50mL), washed with brine (100 mL), dried over magnesium sulfate, filtered and solvent removed in vacuo. The residue was slurried into 10 mL methanol, treated with 10 mL 1N HCl in methanol, and precipitated with 200 mL diethyl ether. The precipitate was collected and dried under vacuum to afford bright yellow solid, 0.312 g (64%): M.P. 259-261°C (dec); LC-MS: 311 (MH⁺), 313 ((M+2)H⁺); Calc C₁₇H₁₅ClN₄·HCl·1.5H₂O: C,54.55; H,5.12; N,14.97; Found: C,54.27; H,5.00; N,14.99

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Example 117N-[4-(6-Chloro-2,3-dihydro-indol-1-yl)-quinazolin-6-yl]-N-methyl formamide

The compound of the preceding Example 116 (0.22 g 0.634 mmol) was reacted in 1 mL of a 50% solution of acetic formic anhydride in acetic acid for one hour and precipitated with 10 mL of ethyl ether. The solid thus obtained was filtered and dried in vacuo to give a yellow solid; 0.14 g (67%) M.P. 178-179°C.

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Example 118N-[4-(6-Chloro-2,3-dihydro-indol-1-yl)-quinazolin-6-yl]-guanidine hydrochloride

4-(6-Chloro-2,3-dihydro-indol-1-yl)-quinazolin-6-ylamine hydrochloride (0.0994g, 0.298 mmol) was slurried into 3 mL 1,2-dichloroethane and treated with triethylamine (0.0415 mL, 0.298 mmol). Acetic acid (0.250 mL, 4.30 mmol) and 3,5-dimethylpyrazole-1-carboxamide (0.0880g, 0.632mmol) were added and the mixture refluxed for 18 hours. After cooling to room temperature, precipitate was collected to afford tan solid, 0.0387 g (35%): M.P. 259-261°C; EI-MS: (high resolution) calc. 338.1047; found 338.1042

20

Example 119N-[4-(6-Chloro-2,3-dihydro-indol-1-yl)-quinazolin-6-yl]-N',N'-dimethyl-propane-1,3-diamine

4-(6-Chloro-2,3-dihydro-indol-1-yl)-quinazolin-6-ylamine hydrochloride (0.525 g, 1.58 mmol) was combined with 2 mL of freshly distilled 3-dimethylaminopropyl chloride and heated to 120°C for 1 hour. Yellow liquid was poured off and the remaining red glass was dissolved in water, basified to pH 11 with potassium carbonate, extracted with chloroform (2 X 50 mL), washed with brine, dried over magnesium sulfate, filtered and stripped to give 0.272 g yellow foam

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containing starting material and mono- and di-alkylated products. This foam was filtered through silica gel using chloroform, then the product was washed through the silica gel with 40% v/v methanol in chloroform and concentrated in vacuo. The residue was dissolved in methanol, treated with 1N HCl in methanol diluted with
5 diethyl ether, filtered and dried under vacuum to afford a bright yellow solid, 0.0995g (15%): M.P. 230°C (dec):LC-MS: 382 (MH⁺), 384 ((M+2)H⁺).

Example 120

4-(6-Chloro-2,3-dihydro-indol-1-yl)-6-morpholin-4-yl-quinazoline

4-Chloro-6-morpholino-quinazoline (382 mg, 1.53 mmol) and 6-chloroindoline
10 (258 mg, 1.63 mmol) were heated at reflux in 8 mL of 1,2-dichloroethane and pyridine (264 mg, 3.36 mmol) for 16 hours. The reaction mixture was vacuum evaporated and partitioned between 100 mL of ethyl acetate and 50 mL of 5% sodium bicarbonate. The organic layer was washed with an additional 50 mL of bicarbonate and 50 mL of brine, dried with magnesium sulfate, filtered and
15 evaporated in vacuo to a residue. This was purified by flash chromatography on silica gel eluted with 20% acetone/methylene chloride. The pure solid isolated from the column was converted to its hydrochloride salt by dissolution in methanol containing 1.1 equivalents of anhydrous hydrogen chloride and precipitation with ether; 396 mg (65%); M.P. 277-279°C.

20

Example 121

4-(6-Chloro-2,3-dihydro-indol-1-yl)-6-(4-methyl-piperazin-1-yl)-quinazoline

4-Chloro-6-(4-methylpiperazin-1-yl)-quinazoline hydrochloride (537 mg, 1.80 mmol) and 6-chloroindoline (169 mg, 1.10 mmol) were refluxed in 10 mL of 1,2-dichloroethane and pyridine (350 mg, 4.40 mmol) for 48 hours. The product was
25 isolated as the hydrochloride using the analogous method of Example 120; 267 mg (58%); M.P. 289-290°C.

Example 122

4-(6-Fluoro-7-methyl-2,3-dihydro-indol-1-yl)-6,7-dimethoxy-quinazoline hydrochloride salt

30 Utilizing a procedure analogous to that described in Example 47 (with conversion to the HCl salt analogous to Example 2), this product was prepared in 58% yield from 6-fluoro-7-methyl-indoline (1.1 eq.), and 4-chloro-6,7-dimethoxy-

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quinazoline (1.0 eq) in N-methyl-pyrrolidinone. (M.P. 220-225° C ; LC-MS: 340 (MH⁺); anal. RP18-HPLC RT: 4.63 min.).

Example 123

1-(6,7-Dimethoxy-quinazolin-4-yl)-2,3,6,7,8,9-hexahydro-1H-benzo[g]indole

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hydrochloride salt

Utilizing a procedure analogous to that described in Example 47 (with conversion to the HCl salt analogous to Example 2), this product was prepared in 58% yield from 2,3,6,7,8,9-hexahydro-1H-benzo[g]indole (1.1 eq.), and 4-chloro-6,7-dimethoxy-quinazoline (1.0 eq) in N-methyl-pyrrolidinone. (M.P. 182-185° C ; LC-MS: 362 (MH⁺); anal. RP18-HPLC RT: 5.26 min.).

Example 124

6,7-Dimethoxy-4-(6-trimethylsilanylethynyl-2,3-dihydro-indol-1-yl)-quinazoline

Utilizing a procedure analogous to that described in Example 47, this product was prepared in 93% yield from 6-trimethylsilanylethynyl-indoline (1.1 eq.), and 4-chloro-6,7-dimethoxy-quinazoline (1.0 eq) in N-methyl-pyrrolidinone. (LC-MS: 404 (MH⁺); anal. RP18-HPLC RT: 6.49 min.).

Example 125

4-(6-Ethynyl-2,3-dihydro-indol-1-yl)-6,7-dimethoxy-quinazoline

To 6,7-dimethoxy-4-(6-trimethylsilanylethynyl-2,3-dihydro-indol-1-yl)-quinazoline (1 eq.; 50 mg; 0.124 mmol) in MeOH (2 mL)/THF (2 mL) was treated with 1M tetrabutylammonium fluoride (2 eq.; 0.248 mL) in THF at 20°C for 16 hours. Solvents were removed in vacuo and the residue was dissolved in 1:1 EtOAc/Et₂O, washed with saturated aqueous NaHCO₃, dried over Na₂SO_{4(s)}, filtered and concentrated in vacuo. The product was converted to the HCl salt using a procedure analogous to that described for Example 2. (M.P. 241-243°C; LC-MS: 332 (MH⁺); RP18-HPLC RT: 4.48 min)

Example 126

4-(6-Chloro-2,3-dihydro-indol-1-yl)-7-difluoromethoxy-quinazoline

To 4-(6-chloro-2,3-dihydro-indol-1-yl)-quinazolin-7-ol (250 mg, 0.84 mmol; from Example 65) in DMF (8mL) was added KF (49 mg, 0.84 mmol) and K₂CO₃ (120 mg). Chlorodifluoromethane (Freon22®) was bubbled into the stirred mixture at 0-5°C for 5-10 minutes in a pressure tube. The tube was sealed and heated with stirring to 80°C for 4 hours after which time anal. RP-HPLC detected no remaining

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starting material. Extractive work-up and flash chromatography on silica (30% acetone/hexanes) as outlined for Example 78 afforded 151 mg (52%) of the difluoromethoxy product which was converted to its hydrochloride salt as outlined in Example 2. (M.P. 250-256°C (dec); LC-MS: 348 (MH⁺); RP18-HPLC RT: 5.64 min)

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Example 127

1-(6,7-Dimethoxy-quinazolin-4-yl)-1,2,3,5-tetrahydro-pyrrolo[2,3-f]indole

Utilizing a procedure analogous to that described in Example 24 (with conversion to its HCl salt using a procedure analogous to that described in Example 2), this product was prepared in 67% yield from 1,2,3,5-tetrahydro-pyrrolo[2,3-f]indole (1.1 eq.), and 4-chloro-6,7-dimethoxy-quinazoline (1.0 eq) in DMF. (M.P. 245-252°C; LC-MS: 347 (MH⁺); RP18-HPLC RT: 3.67 min)

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Example 128

1-(6,7-Dimethoxy-quinazolin-4-yl)-1,2,3,5,6,7-hexahydro-pyrrolo[2,3-f]indole

Utilizing a procedure analogous to that described in Example 24, this product was prepared in 65% yield from 1,2,3,5,6,7-hexahydro-pyrrolo[2,3-f]indole (1.7 eq.), and 4-chloro-6,7-dimethoxy-quinazoline (1.0 eq) in DMF. (LC-MS: 349 (MH⁺); RP18-HPLC RT: 3.51 min)

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Example 129

{3-[1-(6,7-Dimethoxy-quinazolin-4-yl)-2,3-dihydro-1H-indol-3-yl]-propyl}-dimethyl-amine

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Utilizing a procedure analogous to that described in Example 24 (with conversion to its HCl salt using a procedure analogous to that as described in Example 2), this product was prepared in 52% yield from 3-(N,N-dimethylamino-propyl)indoline (1.1 eq.), and 4-chloro-6,7-dimethoxy-quinazoline (1.0 eq) in DMF. (M.P. 230-232°C; LC-MS: 393 (MH⁺); anal. RP18-HPLC RT: 3.23 min.).

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Preparations

Indolines from Indoles

ZnBH₄ Mediated Reduction of Indoles to Indolines

Preparation 1

30

6-Methyl-indoline

6-Methylindole (2.785g, 21.2 mmol) in dry Et₂O (30 mL) was chilled to 0°C and a solution of ZnBH₄ in Et₂O (~ 1.5 eq.; 215 mL of 0.15 M) was added. The mixture was stirred 3 days at 22°C in darkness and then quenched by addition of

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1M aqueous HCl (until no further $H_{2(g)}$ evolved on mixing) followed by basification to pH >10 with 2N NaOH. The ether phase was separated and washed with brine, dried over $MgSO_{4(s)}$, filtered, and concentrated in vacuo to afford >90% pure 6-methyl-indoline as a syrup (2.82g; GC/MS: RT= 0.63 min., $M^+ = 133$). This material
 5 can be purified by chromatography on silica (25% EtOAc/hexanes) or vacuum distillation but was typically used without further purification.

The following indolines were prepared in an analogous manner from the appropriately substituted indoles:

	<u>Prep. #</u>	<u>Indoline Product</u>	<u>Yield</u>	<u>GC/MS</u> <u>RT(min)</u>	<u>GC/MS</u> <u>M^+</u>
10	2	4-Methyl	82%	0.54	133
	3	5-Fluoro	82%	0.54	137
	4	6-Bromo*	90%	1.12	197, 199
	5	6-Benzoyloxy	83%	3.88	225
15	6	6-Methoxy	81%	0.94	149
	7	5-Chloro	72%	0.86	153
	8	5-Methyl	69%	0.62	133
	10	7-Methyl	89%	0.59	133
	11	5,6-Methylene-dioxy	76%	1.18	163
20	12	4-Chloro	85%	0.806	153

*6-Bromoindole was prepared by the Batcho-Leimgruber process exactly as described by Moyer, M. P. et al, J. Org. Chem. 51, 5106-5110 (1986).

Borane/Pyridine Mediated Reduction of Indoles:

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Preparation 13

5-Methoxy-indoline

To 5-methoxy-indole (4.55 g, 31 mmol) suspended in THF (10 mL) at 0-5°C was added borane/pyridine complex (15.5 ml of 8M in BH_3) followed by dropwise aqueous 6N HCl (50 mL) over 15 min. During the addition THF was added
 30 dropwise as required to control foaming. The mixture was stirred 45 min at 20°C, the pH was raised to ~10 by the addition of aqueous NaOH and Na_2CO_3 , and the mixture was extracted with $CHCl_3$. The organic extracts were washed with brine at

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pH 9-10 dried over $\text{MgSO}_{4(\text{a})}$, filtered, and concentrated in vacuo to afford 5-methoxy-indoline (96%; GC-MS: RT= min, $\text{M}^+ = 149$) which was >97% purity by ^1H NMR.

This material could be used without further purification, or precipitated pure as its hydrochloride salt by the addition of 1 eq. of 1N HCl in Et_2O to a solution of the free

5 base in EtOAc or ether.

The following indolines were prepared in an analogous manner by treatment of the appropriately substituted indoles with 4-6 eq. of borane/pyridine complex (with 5-hydroxy-indole starting materials generated according to the procedure described below when necessary).

10	<u>Preparation #</u>	<u>Indoline Product</u>	<u>Yield</u>	<u>GC/MS</u>	<u>GC/MS</u>
				<u>RT (min)</u>	<u>M^+</u>
	14	5,7-dichloro	22%	-	189*
	15	6,7-dimethyl	59%	0.82	147
	16	6-fluoro-7-methyl	56%	0.93	151
15	17	6,7,8,9-tetrahydro-1H-benzo[g]	90%	1.56	173
	18	6-chloro-5-nitro	56%	-	199*
	19	5-hydroxy	91%	1.05	135
	20	5-hydroxy-6-methyl	74%	2.94	149
	21	5-hydroxy-7-methyl	57%	2.83	149
20	22	6-chloro-5-hydroxy	81%	2.89	169
	23	5-hydroxy-6,7-dimethyl	55%	1.67	163
	24	3-(N,N-dimethyl-amino)propyl	91%	-	205*

* MH^+ as observed by LC-MS.

Preparations of Indoles from Anilines

25

Preparation 25

6,7-Dimethylindole

To a solution of boron trichloride (200 mL of 1M in xylene; 200 mmol) at 0-5°C was added 2,3-dimethylaniline (22.2 mL, 182 mmol) in dry toluene (110 mL) dropwise over 20 minutes, followed by 2-chloroacetonitrile (13.8 mL, 218 mmol)

30 dropwise over 10 minutes, and finally AlCl_3 (27.0 g, 202 mmol) in one portion. The

-67-

mixture was heated to reflux for 1 hour and 80°C for 16 hours before cooling and addition of 2N HCl (190 ml). The mixture was heated to 80°C for 30 min, cooled to 20°C, and the pH adjusted to 3-4 with 2N NaOH. The mixture was extracted with CH₂Cl₂ with readjustment of the pH to 3-4 after each extraction. The organic
5 extracts were pooled, washed with brine, dried over Na₂SO_{4(a)}, filtered and concentrated in vacuo. The residue (28.9 g) was recrystallized from CHCl₃/hexanes to afford 26.1 g of pure 2-amino-3,4-dimethyl- α -chloroacetophenone (GC-MS: 197 (M⁺)). This chloromethylketone (5.02 g, 25.4 mmol) in dioxane (125 mL)/H₂O (15 mL) was treated with NaBH₄ (1.06 g, 28 mmol) and heated to reflux for 4 hours. The
10 mixture was concentrated in vacuo and partitioned between H₂O/CH₂Cl at pH ~7. The organic extracts were pooled, dried over MgSO_{4(a)}, filtered and concentrated in vacuo to afford the crude indole product (2.9 g) which could be reduced directly or sublimed in vacuo to afford 1.55 g of the title compound so pure indole (GC-MS; 145 (M⁺)).

15

Preparation 26

6,7,8,9-Tetrahydro-1H-benzo[g]indole

This material was prepared from 5,6,7,8-tetrahydronaphthyl-1-amine via the α -chloroacetophenone intermediate in 76% overall yield utilizing a procedure analogous to that described above for Preparation 25 (GC-MS: 171 (M⁺)).

20

Preparation 27

6-Fluoro-7-methylindole

This material was prepared from 3-fluoro-2-methylaniline via its α -chloromethyl ketone derivative in 46% overall yield utilizing a procedure analogous to that described above for Preparation 25 ((GC-MS: 149 (M⁺)).

25

Preparation of Substituted Isatins from the Corresponding Anilines and BH₃/THF Mediated Reduction of Oxindoles and Isatins to Indoles:

Preparation 28

1,2,3,5-Tetrahydro-pyrrolo[2,3-f]indole

A solution of 1-acetyl-5-amino-indoline (4.94 g, 28.03 mmol) in conc. HCl
30 (250 mL) and H₂O (17 mL) was added to a mixture of chloral hydrate (5.12 g, 31.0 mmol), and Na₂SO₄ (73.8 g, 0.52 mol) in H₂O (68 mL). Once all materials were dissolved, hydroxylamine hydrochloride (6.27 g, 190 mmol) was added and the solution was heated to boiling over 30 minutes and maintained at a boil for 30

-68-

minutes. The precipitate which formed upon cooling to 20°C was removed by filtration, washed with H₂O, and dried in vacuo to constant mass to afford 6.68 g. of the 1-acetyl-5-[2-(isonitroso)acetamido]indoline (LC-MS: 248 (MH⁺)). This material was added in small portions over 30 minutes to conc. H₂SO₄ (20 mL) while stirring at 50°C. When the addition was complete the mixture was heated to 80°C for 10 minutes, cooled to 20°C, and poured into ice/water (300 mL). The precipitate was filtered, washed with H₂O and dried in vacuo to yield 6.02 g of the 1-acetyl isatin derivative (LC-MS: 248 (M+NH₄⁺)). A sample (2.68 g, 11.4 mmol) of this product was heated to 50°C in dioxane (23 mL)/6N HCl (25 mL) for 16 hours. Concentration of the mixture in vacuo at 40°C yielded the crude deacetyled isatin product (LC-MS: 189 (MH⁺)) which was redissolved in THF (50 mL) and reduced directly by addition of 1M borane/THF (114 mL, ~ 10 eq.). After stirring 16 hours at 20°C the mixture was carefully quenched with H₂O (50 mL), diluted with brine, and the pH adjusted to 10-11 before extraction with EtOAc. The organic extracts were pooled, dried over Na₂SO_{4(s)}, filtered and concentrated in vacuo. The residue was recrystallized from Et₂O/hexanes to afford pure 1,2,3,5-tetrahydro-pyrrolo[2,3-f]indole (797 mg, LC-MS: 159 (MH⁺)).

Preparation 29

6-Chloro-5-fluoro-indole

To a solution of 6-chloro-5-fluoro-oxindole (0.49 g, 2.64 mmol) in THF (5 mL) was added slowly 1M BH₃ in THF (21.2 mL, 21.2 mmol) over 30 minutes. The mixture was stirred 24 hours and 1N aqueous NaOH (25 mL) was added carefully with stirring. After stirring 20 minutes the mixture was extracted with EtOAc/Et₂O (1:1), and the extracts were combined, washed with brine, dried over Na₂SO_{4(s)}, filtered and concentrated in vacuo to afford 412 mg of the product as a mixture of 6-chloro-5-fluoroindole and 6-chloro-5-fluoroindoline (GC-MS: 169, and 171 (M⁺), respectively), which was used without further purification.

Preparation 30

5,6-Dichloro-indole

This material was produced in 93% yield from 5,7-dichloro-isatin (1 eq) and BH₃/THF (6 mol eq.) utilizing a method analogous to that described for 6-chloro-5-fluoro-indole (Preparation 29).

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Preparation 316-Chloro-5-nitro-indole

This material was produced from 6-chloro-5-nitro-oxindole (1 eq) and BH_3/THF (6 mol eq.) utilizing a method analogous to that described for 6-chloro-5-fluoro-indole (Preparation 29) in 99% yield (contaminated with some 6-chloro-5-nitro-indoline) and used directly in the subsequent borane/pyridine reduction.

Preparation of 5-Hydroxyindoles from Appropriately Substituted Indolines:Preparation 325-Hydroxy-6-methyl-indole

10 Potassium nitrosodisulfonate (1.18 g, 4.4 mmol, 2.2 eq.) in pH 7.0, 0.10M potassium phosphate buffer (80 mL) was added to 6-methyl-indoline (266 mg, 2.0 mmol) in acetone (25 mL) at 20°C. The mixture was stirred for 15 min.. and extracted with CHCl_3 (4 X 40 mL). The organic layer was washed with brine, dried over Na_2SO_4 , and concentrated in vacuo to afford 290 mg of crude product as
15 purple solid (~80% purity by ^1H NMR; GC-MS: 147 (M^+)) which was used without further purification.

Preparation 336-Chloro-5-hydroxy-indole

Chilled potassium nitrosodisulfonate (7.69 g, 28.6 mmol, 2.2 eq.) in pH 7.0,
20 0.13M potassium phosphate buffer (520 mL) was added to 6-chloroindoline (2.0 g, 13 mmol) in acetone (110 mL) at 0°C. The mixture was stirred at 0°C for 1 hour and extracted with CHCl_3 (250 mL, then 2 X 75 mL). The organic layer was washed with brine, dried over Na_2SO_4 , and concentrated in vacuo to afford 2.34 g of purple solid. This mixture of 6-chloroindoline, 6-chloroindole, and 6-chloro-5-hydroxyindole
25 was partitioned between degassed aqueous 1N NaOH (150 mL) and ether (3 X 25 mL). The pH of the aqueous phase was adjusted to ~4 with acetic acid and the desired 6-chloro-5-hydroxy-indole (460 mg; GC-MS: 167 (M^+)) was recovered by extraction with CHCl_3 and used without further purification.

Preparations 34 & 35

30 5-Hydroxy-7-methyl-indole and 5-Hydroxy-6,7-dimethyl-indole

These intermediates were prepared from 7-methylindoline and 6,7-dimethylindoline in 73% and 68% yields, respectively, utilizing the procedure described for 5-hydroxy-6-methyl-indole above (Preparation 32).

Brominations of Indolines and Larger Annelated-anilines**Preparation 36****8-Bromo-2,3,4,5-tetrahydro-1H-benzo[b]azepine**

- To 2,3,4,5-tetrahydro-1H-benzo[b]azepine (410 mg, 2.78 mmol; from
- 5 Preparation 41) in conc. H_2SO_4 (5 mL) was added Ag_2SO_4 (438 mg, 1.41 mmol). The mixture was stirred until the silver sulfate had dissolved and then $\text{Br}_{2(l)}$ (145 μL , 2.80 mmol) was added at 0-5°C over 15 minutes. The mixture was stirred in the dark and allowed to warm to 20°C. After 4 hours the mixture was poured into ice/ H_2O (50 mL), the pH was adjusted to 12-14 by the careful addition of 6N KOH
- 10 with cooling, and then filtered through a pad of Celite. The pad was washed with CH_3CN , CHCl_3 , and Et_2O . The aqueous phase was extracted with EtOAc and the organic extracts and washes were combined, dried over $\text{MgSO}_{4(s)}$, filtered and concentrated in vacuo to afford 468 mg of a waxy yellow solid. The 6-bromo (48 mg) and 8-bromo isomers (492 mg; GC-MS: 226, 228 (M^+)) were separated by flash
- 15 chromatography on silica (10% EtOAc /hexanes) and/or recrystallization (Et_2O /Hexanes).

Alternative Indoline Preparations:**Preparation 37****6-Iodo-indoline**

- 20 To a stirred slurry of 1-acetyl-6-amino-indoline (17.6g, 100 mmol) in H_2O (100 mL) was added concentrated H_2SO_4 (12.5 mL). After stirring 10 minutes the solution was cooled to 0-5°C and NaNO_2 (6.91g, 100 mmol) in H_2O (25 mL) was added dropwise over 1 hour. A freshly prepared solution of KI (20.04g, 121 mmol) in 1M H_2SO_4 (20 mL) was added dropwise to the dark brown solution with stirring at 0-
- 25 10°C. The mixture was allowed to warm to 22°C for ~30 min., and then the solution was heated to 55°C until no further production of $\text{N}_{2(g)}$ was evident. After cooling the pH was adjusted to ~11 and the mixture was extracted with CHCl_3 (3 X 150 mL). Organic extracts were pooled, washed with brine, dried over $\text{MgSO}_{4(s)}$, filtered and concentrated in vacuo. The residue containing 1-acetyl-6-iodo-indoline
- 30 was treated with KOH (14g, 250 mmol) in refluxing MeOH (170 mL) with THF (30 mL) in an $\text{N}_{2(g)}$ atmosphere for 72 hours. After cooling, HOAc (9g, 150 mmol) was added and the mixture was concentrated in vacuo. The residue was partitioned between CHCl_3 (400 mL) and 5% aqueous NaHCO_3 (250 mL), and the organic

-71-

phase was dried over $\text{MgSO}_{4(\text{s})}$, filtered, and concentrated in vacuo. The residue was chromatographed on silica in 30% EtOAc/hexanes to afford pure 6-iodo-indoline (8.7g; GC/MS: RT = 1.51 min., $M^+ = 245$) as tan crystals.

Preparation 38

5

6-Trimethylsilylanylethynyl-indoline

6-Iodo-indoline (499 mg, 2.04 mmol) was added to a mixture of CuI (77.5 mg, 0.407 mmol), $\text{Pd}(\text{PPh}_3)_4$ (113 mg, 0.097 mmol), and trimethylsilylacetylene (0.432 mL, 3.06 mmol) in degassed Et_2NH (10 mL). The mixture was stirred at reflux under $\text{N}_{2(\text{g})}$ for 30 minutes. Solvent was removed in vacuo and the residue was flash
10 chromatographed on silica (25% EtOAc/hexanes) to afford 364 mg of pure 6-trimethylsilylanylethynyl-indoline (GC-MS: 215 (M^+)).

Preparation 39

6-Chloro-indoline

This material was conveniently prepared on multigram scale from the
15 cyclization of 2,4-dichlorophenethylamine in the presence of $\text{Na}_2\text{CO}_3(\text{s})$ (1.2 mol eq), Cu_2Cl_2 (0.01 mol eq) and 8-hydroxyquinoline (0.012 mol eq) in isoamyl alcohol (1 vol) at 130°C for 5 hours. After addition of hydrazine (0.0055 vol) and 1 hour reflux, the mixture was filtered, solvent was removed in vacuo (45°C @ ~10mm Hg) and 6-chloro-indoline was obtained pure by vacuum distillation ($95\text{--}100^\circ\text{C}$ @ 2mm
20 Hg)(65-95%).

Preparation 40

DL-Indoline-2-carboxylic Acid Methyl Ester

DL- Indoline-2-carboxylic acid (3.16g, 19.4 mmol) was suspended in MeCN (50 mL) with stirring and treated with an ethereal solution of CH_2N_2 (~0.5M) until no
25 further evolution of $\text{N}_{2(\text{g})}$ resulted on further additions and the yellow color of the reagent persisted. The solution was concentrated in vacuo and the residue was taken up in EtOAc (150 mL), washed with saturated aqueous NaHCO_3 (3 X 50 mL) and brine, dried over $\text{MgSO}_{4(\text{s})}$, filtered and concentrated in vacuo to an oil containing >95% pure methyl ester (3.36g; GC/MS: 177 (M^+)) which was used
30 without further purification.

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Larger Annelated-Aniline SystemsPreparation 412,3,4,5-Tetrahydro-1H-benzo[b]azepine

To a solution of 2,3,4,5-tetrahydro-1H-1-benzo[b]azepin-2-one (0.776 g, 4.81 mmol) in THF (10 mL) was added 1M BH₃ in THF (38.5 ml, 38.5 mmol; 8 eq.) dropwise over 30 minutes at 0°C. The solution was stirred 24 hours at 20°C and quenched by the dropwise addition of H₂O (40 mL). The mixture was diluted with brine and extracted with EtOAc/Et₂O (2:1). The organic extracts were washed with 1N NaOH, pooled, dried over MgSO₄(s), filtered and concentrated in vacuo to afford 703 mg (~99%) of crude product (GC-MS: 147 (M⁺)) which was used without further purification.

Preparation 42

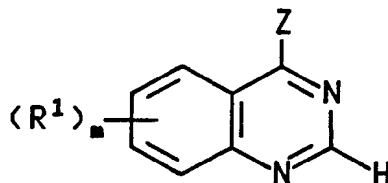
1,2,3,4,5,6-Hexahydro-benzo[b]azocine was prepared by the BH₃/THF mediated reduction of the 1,2,3,4,5,6-hexahydro-1-benzo[b]azocin-2-one in a manner analogous to that described above for preparation 41.

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CLAIMS

1. A compound of Formula I

5



Formula I

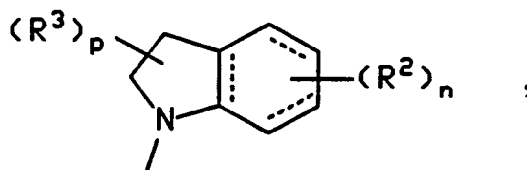
and the pharmaceutically acceptable salts and stereoisomers thereof

10 wherein either A, B or C

A:

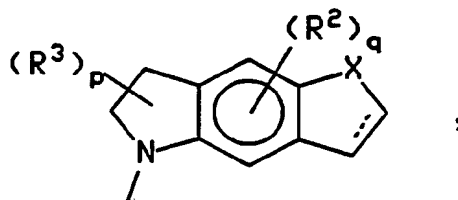
Z is

15



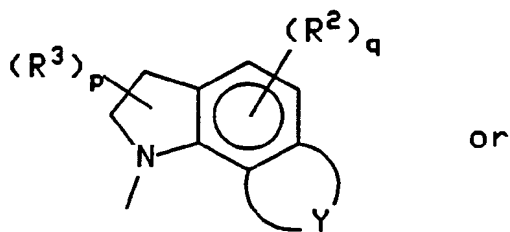
Formula II

20



Formula III

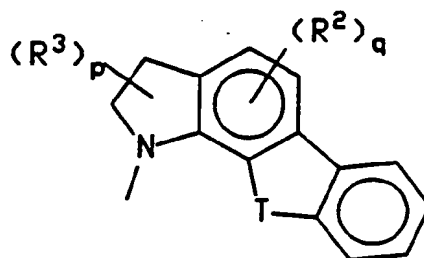
25



30

Formula IV

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Formula V

wherein

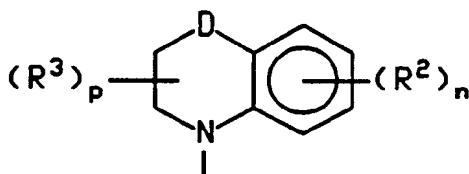
X is methylene, thio, -N(H)- or oxy;

Y completes a 5 or 6 membered aromatic, or partially saturated ring which may incorporate an oxygen or sulfur atom;

T is methylene, -N(H)-, thio or oxy;

B:

Z is



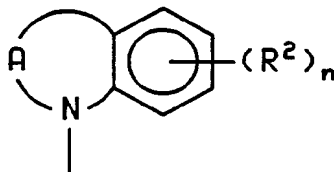
Formula VI

wherein D may be saturated carbon, oxy or thio;

or

C:

Z is



Formula VIII

wherein A completes a 7 to 9 membered mono-unsaturated mono-aza ring;

R¹ for each occurrence is independently

-75-

- a. trifluoromethyl, halo, nitro, hydroxy, amino, cyano, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₁-C₄)alkoxycarbonyl, (C₁-C₄)alkanoyloxy, (C₁-C₄)alkanoylamino, carboxy, phenoxy, benzoyloxy, carbamoyl, mono-N- or di-N,N-di-(C₁-C₄)alkylcarbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylamino, mono-N or di-N,N-(hydroxy(C₂-C₄)alkyl)amino, mono-N or di-N,N-((C₁-C₄)alkoxy(C₂-C₄)alkyl)amino, anilino, pyrrolidin-1-yl, piperidin-1-yl, morpholino, piperazin-1-yl, 4-(C₁-C₄)alkylpiperazin-1-yl, (C₁-C₄)alkylthio, phenylthio, or such groups substituted on (C₁-C₄)alkyl;
- b. hydroxy(C₂-C₄)alkoxy(C₁-C₄)alkyl, (C₁-C₄)alkoxy-(C₂-C₄)alkoxy-(C₁-C₄)alkyl, hydroxy(C₂-C₄)alkylthio(C₁-C₄)alkyl, (C₁-C₄)alkoxy(C₂-C₄)alkylthio(C₁-C₄)alkyl, hydroxyamino, benzoylamino, mono-N or di-N,N-(C₁-C₄)alkylcarbamoylmethylamino, carbamoylmethylamino, (C₁-C₄)alkoxycarbonylamino, (C₁-C₄)alkanoylamino, carboxymethylamino, (C₁-C₄)alkoxycarbonylmethylamino, (C₁-C₄)alkoxyamino, (C₂-C₄)alkanoyloxyamino, phenyl(C₁-C₄)alkylamino, (C₁-C₄)alkylsulphonylamino, benzenesulphonamido, 3-phenylureido, 2-oxopyrrolidin-1-yl, 2,5-dioxopyrrolidin-1-yl, ureido, (C₁-C₄)alkoxy(C₁-C₄)alkylcarbonylamino, (C₁-C₄)alkylsulfinyl, (C₁-C₄)alkylsulfonyl, (C₁-C₄)alkoxy(C₂-C₄)alkylthio, mono-, di- or trifluoromethyloxy, (C₁-C₄)alkylenedioxy, benzyloxy, azido, guanidino, aminocarbonyl, mono-N- or di-N,N-(C₁-C₄)alkylaminocarbonyl, phenyl(C₁-C₄)alkoxy, carboxymethoxy, (C₁-C₄)alkoxycarbonylmethoxy, carbamoylmethoxy, mono-N or di-N,N-(C₁-C₄)alkyl carbamoylmethoxy, mono-N- or di-N,N-(hydroxy(C₂-C₄)alkyl)carboxamido, mono-N- or di-N,N-((C₁-C₄)alkoxy (C₂-C₄)alkyl)carboxamido or bis((C₁-C₄)alkanesulfonyl)amido; or
- c. (C₂-C₄)alkoxy, (C₂-C₄)alkylthio, (C₂-C₄)alkanoyloxy, (C₂-C₄)alkylamino, (C₁-C₄)alkyl(C₁-C₄)alkylenedioxy, or (C₂-C₄)alkanoylamino; each such group substituted with amino, halo, hydroxy, (C₂-C₄)alkanoyloxy, (C₁-C₄)alkoxy, mono-N- or di-N,N-(C₁-C₄)alkylamino, mono-N or di-N,N-(hydroxy(C₂-C₄)alkyl)amino, mono-N or di-N,N-((C₁-C₄)alkoxy(C₂-C₄)alkyl)amino, (C₁-C₄)alkanoylamino, phenoxy, anilino, imidazol-1-yl, phenylthio, piperidino, morpholino, piperazin-1-yl, 4-(C₁-C₄)alkylpiperazin-1-yl, carboxy, (C₁-C₄)alkoxycarbonyl, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, carboxamido, mono-N- or di-N,N-(C₁-C₄)alkylcarboxamido or mono-N- or di-N,N-(hydroxy(C₂-C₄)alkyl)carboxamido;

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wherein any phenyl in a R^1 substituent is optionally mono- or di- substituted with halo, nitro, trifluoromethyl, hydroxy, (C_1-C_4) alkoxy or (C_1-C_4) alkyl and said (C_1-C_4) alkylenedioxy is linked at both ends to the quinazoline moiety;

- R^2 for each occurrence is independently mono-, di- or tri-fluoromethyl, halo, nitro, hydroxy, amino, azido, isothiocyano, (C_1-C_4) alkyl, phenyl, thienyl, (C_1-C_4) alkoxy, benzyloxy, phenoxy, (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, (C_1-C_4) alkylenedioxy, cyano, benzoylamino, trifluoromethylcarbonylamino, (C_1-C_4) alkanoylamino, (C_1-C_4) alkanoyl, N-mono- or N,N-di- (C_1-C_4) alkylamino, (C_1-C_4) alkylsulfonylamino, trifluoromethylsulfonylamino, (C_1-C_4) alkylthio, (C_1-C_4) alkylsulfanyl or (C_1-C_4) alkylsulfonyl, pyrrol-1-yl, piperidin-1-yl or pyrrolidin-1-yl, said phenyl, benzyloxy, phenoxy and benzoylamino optionally mono-substituted with halo, nitro, trifluoromethyl, hydroxy or (C_1-C_4) alkyl and said (C_1-C_4) alkylenedioxy is linked at both ends to adjacent carbons on the benzene moiety;

- R^3 for each occurrence is independently hydroxy, amino, N-mono- or N,N-di- (C_1-C_4) alkylamino, sulfo, or (C_1-C_4) alkoxy (provided that such groups are not attached to a ring carbon which is adjacent to an oxy, thio or -N-), or R^3 for each occurrence is independently carboxy, hydroxy (C_1-C_4) alkyl, (C_1-C_4) alkoxy (C_1-C_4) alkyl, amino (C_1-C_4) alkyl, mono-N- or di-N,N- (C_1-C_4) alkylamino (C_1-C_4) alkyl, morpholino (C_1-C_4) alkyl, 4- (C_1-C_4) alkyl-piperazin-1-yl (C_1-C_4) alkyl, carboxy (C_1-C_4) alkyl, (C_1-C_4) alkoxycarbonyl, sulfo (C_1-C_4) alkyl or (C_1-C_4) alkyl;

where m is 0-3;

n is 0-4;

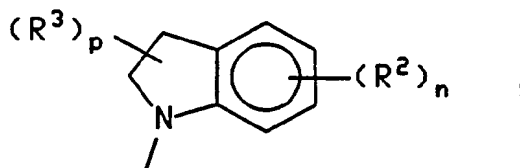
p is 0, 1 or 2; and

q is 0, 1 or 2;

- with the proviso that 4-(3,4-dihydro-2H-quinolin-1-yl)-quinazoline is not included.

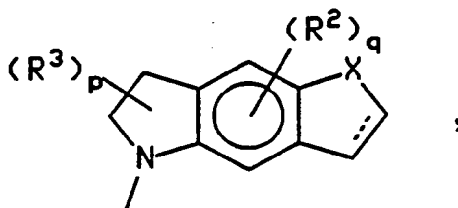
2. A compound as recited in claim 1 wherein

Z is

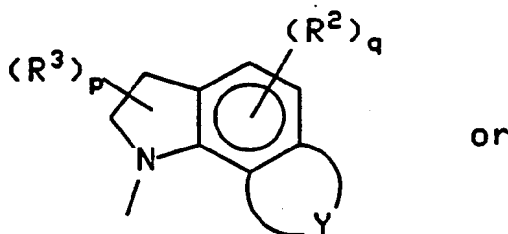


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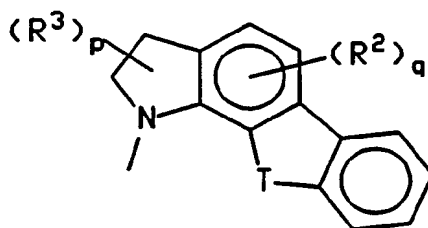
-77-



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10



15

R¹ for each occurrence is independently hydroxy, (C₁-C₄)alkoxy, hydroxy(C₂-C₄)alkoxy, amino(C₂-C₄)alkyl, amino(C₂-C₄)alkoxy, (C₁-C₄)alkoxy(C₂-C₄)alkoxy, (C₁-C₄)alkylenedioxy, hydroxy(C₁-C₄)alkyl(C₁-C₄)alkylenedioxy, (C₁-C₄)alkoxy(C₁-C₄)alkyl(C₁-C₄)alkylenedioxy, mono-N- or di-N,N-(C₁-C₄)alkylamino(C₂-C₄)alkoxy, 3- or 4-(C₁-C₄)alkoxy-(2-hydroxy)-(C₃-C₄)alkoxy, carboxy(C₁-C₄)alkoxy, morpholino(C₂-C₄)alkoxy, imidazol-1-yl(C₂-C₄)alkoxy, 4(C₁-C₄)alkylpiperazin-1-yl-(C₂-C₄)alkoxy, (C₁-C₄)alkoxy(C₁-C₄)alkanoyloxy, nitro, hydroxylamino, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, (C₁-C₄)alkanoylamino, hydroxy(C₂-C₄)alkylamino, (C₁-C₄)alkoxy(C₂-C₄)alkylamino, (C₁-C₄)alkylsulfonamido, morpholino, (C₁-C₄)alkyl-piperazin-1-yl, bis(C₁-C₄)alkanesulfonamido, di(C₁-C₄)alkylamino(C₂-C₄)alkylamino, (C₁-C₄)alkylamino(C₂-C₄)alkylamino, imidazol-1-yl, piperidin-1-yl, pyrrolidin-1-yl, (C₁-C₄)alkoxy(C₁-C₄)alkylcarbonylamino, N-(C₁-C₄)alkyl-N-(C₁-C₄)alkanoyl-amino, carboxy, (C₁-C₄)alkoxycarbonyl, (C₁-C₄)alkoxycarbonyl(C₁-C₄)alkoxy, amido, mono-N- or di-N,N-(C₁-C₄)alkylaminocarbonyl, mono-N- or di-N,N-(hydroxy(C₂-C₄)alkyl)aminocarbonyl, (C₁-C₄)alkyl, hydroxy(C₁-C₄)alkyl, mono-N- or di-N,N-((C₁-

-78-

C_4)alkoxy(C_1 - C_4)alkyl)amino(C_1 - C_4)alkyl, mono-N- or di-N,N-(C_1 - C_4)alkylamino(C_1 - C_4)alkyl, (C_1 - C_4)alkanoylamino(C_1 - C_4)alkyl, (C_1 - C_4)alkoxy(C_2 - C_4)alkoxy(C_1 - C_4)alkyl, (C_1 - C_4)alkylthio, (C_1 - C_4)alkoxy(C_2 - C_4)alkylthio or hydroxy(C_2 - C_4)alkylthio;

R^2 for each occurrence is independently nitro, halo, (C_1 - C_4)alkyl, pyrrol-1-yl, hydroxyl, amino, mono-N- or di-N,N-(C_1 - C_4)alkylamino, amino(C_1 - C_4)alkyl, azido, ethenyl, ethynyl, (C_1 - C_4)alkylenedioxy, phenyl or (C_1 - C_4)alkylthio;

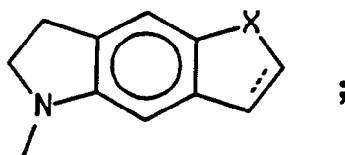
R^3 for each occurrence is independently hydroxy(C_1 - C_4)alkyl, (C_1 - C_4)alkyl, amino(C_1 - C_4)alkyl, carboxy(C_1 - C_4)alkyl or mono-N- or di-N,N-(C_1 - C_4)alkylamino(C_1 - C_4)alkyl;

10 m is 0, 1 or 2;
 p is 0 or 1; and
 n is 0, 1, 2, or 3.

3. A compound as recited in claim 2 wherein

Z is

15



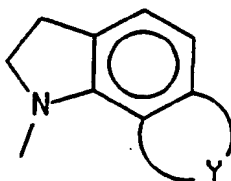
X is -N(H)-; and

20 R^1 for each occurrence is substituted independently in the 6 and/or 7 position.

4. A compound as recited in claim 2 wherein

Z is

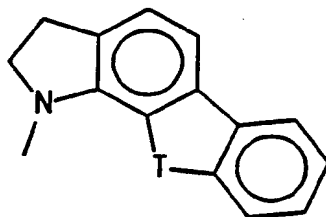
25



30

or

-79-



; and

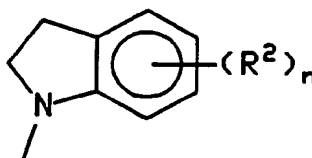
5

R^1 for each occurrence is independently substituted in the 6 and/or 7 position.

5. A compound as recited in claim 2 wherein

10

Z is



15

n is 1, 2 or 3;

m is 1 or 2;

R^1 for each occurrence is substituted independently in the 6 and/or 7 positions and is (C₁-C₄)alkyl, (C₁-C₄)alkoxy, hydroxy(C₂-C₄)alkoxy, (C₁-C₄)alkoxy(C₂-C₄)alkoxy, carboxy(C₁-C₄)alkoxy, (C₁-C₄)alkoxycarbonyl(C₁-C₄)alkoxy, imidazol-1-yl-(C₂-C₄)alkoxy, morpholino(C₂-C₄)alkoxy, 4-(C₁-C₄)alkylpiperazin-1-yl(C₁-C₄)alkoxy, (C₁-C₄)alkoxy-2-hydroxy(C₃-C₄)alkoxy, amino, (C₁-C₄)alkylamino, di-N,N-alkylamino, (C₁-C₄)alkanoylamino, (C₁-C₄)alkylsulfonylamido, morpholino, (C₁-C₄)alkylpiperazin-1-yl, mono-N- or di-N,N-(C₁-C₄)alkylamino(C₂-C₄)alkylamino; and

20

R^2 for each occurrence is independently 4-hydroxy, 4-amino, 5-fluoro, 5-hydroxy, 5-amino, 6-halo, 6-methyl, 6-ethenyl, 6-ethynyl, 6-nitro or 7-methyl.

25

6. A compound according to claim 5 wherein

R^2 for each occurrence is independently halo, nitro, hydroxy or methyl;

R^1 is (C₁-C₄)alkoxy or (C₁-C₄)alkyl;

m is 2; and

30

n is 1 or 2.

7. The compound as recited in claim 5 wherein

m is 2;

R^1 is 6-methoxy;

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R¹ is 7-methoxy;

n is 2 ;

R² is 5-fluoro; and

R² is 6-bromo.

- 5 8. The compound as recited in claim 5 wherein
m is 2;

R¹ is 6-(2-methoxyethoxy);

R¹ is 7-(2-methoxyethoxy) ;

n is 1 ; and

10 R² is 6-chloro.

9. The compound as recited in claim 5 wherein
m is 2;

R¹ is 6-methoxy;

R¹ is 7-(2-hydroxyethoxy);

15 n is 1 ; and

R² is 6-chloro.

10. The compound as recited in claim 5 wherein
m is 1;

R¹ is 6-amino;

20 n is 1; and

R² is 6-chloro.

11. The compound as recited in claim 5 wherein
m is 2;

R¹ is 6-methoxy;

25 R¹ is 7-(3-hydroxypropoxy);

n is 1; and

R² is 6-chloro.

12. The compound as recited in claim 5 wherein
m is 2;

30 R¹ is 7-(2-imidazol-1-yl-ethoxy);

R¹ is 6-methoxy;

n is 1; and

R² is 6-chloro.

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13. The compound as recited in claim 5 wherein

m is 2;

R¹ is 6-methoxy;

R¹ is 7-methoxy;

5 n is 1; and

R² is 5-amino.

14. The compound as recited in claim 5 wherein

m is 2;

R¹ is 6-methoxy;

10 R¹ is 7-(2-methoxy-ethoxy);

n is 2 ;

R² is 5-fluoro; and

R² is 6-bromo.

15. The compound as recited in claim 5 wherein

15 m is 2;

R¹ is 6-methoxy;

R¹ is 7-methoxy;

n is 2;

R² is 5-amino; and

20 R² is 6-chloro.

16. The compound as recited in claim 5 wherein

m is 2;

R¹ is 6-methoxy;

R¹ is 7-(2-hydroxy-3-methoxy)propoxy;

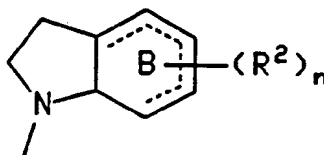
25 n is 1; and

R² is 6-chloro.

17. A compound as recited in claim 1 wherein

Z is

30



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the B six membered ring has 0, 1 or 2 double bonds in the dotted line region;

n is 0-2;

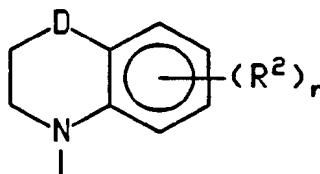
R² for each occurrence is independently halo, hydroxy or (C₁-C₄)alkyl;

5 m is 0, 1 or 2; and

R¹ for each occurrence is substituted independently in the 6 and/or 7 positions and is hydroxy, (C₁-C₄)alkoxy, hydroxy(C₂-C₄)alkoxy, amino(C₂-C₄)alkyl, amino(C₂-C₄)alkoxy, (C₁-C₄)alkoxy(C₂-C₄)alkoxy, (C₁-C₄)alkylenedioxy, hydroxy(C₁-C₄)alkyl(C₁-C₄)alkylenedioxy, (C₁-C₄)alkoxy(C₁-C₄)alkyl(C₁-C₄)alkylenedioxy, mono-N- or di-N,N-(C₁-C₄)alkylamino(C₂-C₄)alkoxy, 3- or 4-(C₁-C₄)alkoxy-(2-hydroxy)-(C₃-C₄)alkoxy, carboxy(C₁-C₄)alkoxy, morpholino(C₂-C₄)alkoxy, imidazol-1-yl(C₂-C₄)alkoxy, 4-(C₁-C₄)alkylpiperazin-1-yl-(C₂-C₄)alkoxy, (C₁-C₄)alkoxy(C₁-C₄)alkanoyloxy, nitro, hydroxylamino, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, (C₁-C₄)alkanoylamino, hydroxy(C₂-C₄)alkylamino, (C₁-C₄)alkoxy(C₂-C₄)alkylamino, (C₁-C₄)alkylsulfonamido, morpholino, (C₁-C₄)alkyl-piperazin-1-yl, bis(C₁-C₄)alkanesulfonamido, di-N,N-(C₁-C₄)alkylamino(C₂-C₄)alkylamino, (C₁-C₄)alkylamino(C₂-C₄)alkylamino, piperidin-1-yl, imidazol-1-yl, pyrrolidin-1-yl, (C₁-C₄)alkoxy(C₁-C₄)alkylcarbonylamino, N-(C₁-C₄)alkyl-N-(C₁-C₄)alkanoyl-amino, carboxy, (C₁-C₄)alkoxycarbonyl, (C₁-C₄)alkoxycarbonyl(C₁-C₄)alkoxy, amido, mono-N- or di-N,N-(C₁-C₄)alkylaminocarbonyl, mono-N- or di-N,N-(hydroxy(C₂-C₄)alkyl)aminocarbonyl, (C₁-C₄)alkyl, hydroxy(C₁-C₄)alkyl, mono-N- or di-N,N-((C₁-C₄)alkoxy(C₁-C₄)alkyl)amino(C₁-C₄)alkyl, mono-N- or di-N,N-(C₁-C₄)alkylamino(C₁-C₄)alkyl, (C₁-C₄)alkanoylamino(C₁-C₄)alkyl, (C₁-C₄)alkoxy(C₂-C₄)alkoxy(C₁-C₄)alkyl, (C₁-C₄)alkylthio, (C₁-C₄)alkoxy(C₂-C₄)alkylthio or hydroxy(C₂-C₄)alkylthio.

25 18. A compound as recited in claim 1 wherein

Z is



30

D is saturated carbon;

n is 0, 1 or 2;

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R^2 for each occurrence is independently halo, hydroxy, amino, nitro, trifluoromethyl, ethenyl, ethynyl or (C_1-C_4) alkyl;

m is 0, 1 or 2; and

R^1 for each occurrence is substituted independently in the 6 and/or 7

- 5 positions and is hydroxy, (C_1-C_4) alkoxy, hydroxy (C_2-C_4) alkoxy, amino (C_2-C_4) alkyl, amino (C_2-C_4) alkoxy, (C_1-C_4) alkoxy (C_2-C_4) alkoxy, (C_1-C_4) alkylenedioxy, hydroxy (C_1-C_4) alkyl (C_1-C_4) alkylenedioxy, (C_1-C_4) alkoxy (C_1-C_4) alkyl (C_1-C_4) alkylenedioxy, mono-N- or di-N,N- (C_1-C_4) alkylamino (C_2-C_4) alkoxy, 3- or 4- (C_1-C_4) alkoxy-(2-hydroxy)- (C_3-C_4) alkoxy, carboxy (C_1-C_4) alkoxy, morpholino (C_2-C_4) alkoxy, imidazol-1-yl $(C_2-$
- 10 $C_4)$ alkoxy, 4- (C_1-C_4) alkylpiperazin-1-yl- (C_2-C_4) alkoxy, (C_1-C_4) alkoxy (C_1-C_4) alkanoyloxy, nitro, hydroxylamino, amino, mono-N- or di-N,N- (C_1-C_4) alkylamino, (C_1-C_4) alkanoylamino, hydroxy (C_2-C_4) alkylamino, (C_1-C_4) alkoxy (C_2-C_4) alkylamino, (C_1-C_4) alkylsulfonamido, morpholino, (C_1-C_4) alkyl-piperazin-1-yl, bis (C_1-C_4) alkanesulfonamido, di (C_1-C_4) alkylamino (C_2-C_4) alkylamino, (C_1-C_4) alkylamino $(C_2-$
- 15 $C_4)$ alkylamino, imidazol-1-yl, piperidin-1-yl, pyrrolidin-1-yl, (C_1-C_4) alkoxy (C_1-C_4) alkylcarbonylamino, N (C_1-C_4) alkyl-N- (C_1-C_4) alkanoyl-amino, carboxy, (C_1-C_4) alkoxycarbonyl, (C_1-C_4) alkoxycarbonyl (C_1-C_4) alkoxy, amido, mono-N- or di-N,N- (C_1-C_4) alkylaminocarbonyl, mono-N- or di-N,N-(hydroxy (C_2-C_4) alkyl)aminocarbonyl, (C_1-C_4) alkyl, hydroxy (C_1-C_4) alkyl, mono-N- or di-N,N- $((C_1-C_4)$ alkoxy $(C_1-$
- 20 $C_4)$ alkyl)amino (C_1-C_4) alkyl, mono-N- or di-N,N- (C_1-C_4) alkylamino (C_1-C_4) alkyl, (C_1-C_4) alkanoylamino (C_1-C_4) alkyl, (C_1-C_4) alkoxy (C_2-C_4) alkoxy (C_1-C_4) alkyl, (C_1-C_4) alkylthio, (C_1-C_4) alkoxy (C_2-C_4) alkylthio or hydroxy (C_2-C_4) alkylthio.

19. A compound according to claim 18 wherein

- 25 R^2 for each occurrence is independently halo, nitro, hydroxy, (C_1-C_4) alkyl or trifluoromethyl;

R^1 is (C_1-C_4) alkoxy, (C_1-C_4) alkylenedioxy or (C_1-C_4) alkyl;

m is 2; and

n is 1 or 2.

20. A method of treating hyperproliferative disorders which comprises administering
- 30 to a mammal in need of such treatment a hyperproliferative disorder treating amount of a compound of claim 1.

21. A method as recited in claim 20 wherein the hyperproliferative disease is cancer.

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22. A method as recited in claim 21 wherein the disease is brain, lung, squamous cell, bladder, gastric, pancreatic, hepatic, renal, colorectal, breast, head, neck, oesophageal, gynecological or thyroid cancer.

23. A method as recited in claim 20 wherein the hyperproliferative disorder is
5 noncancerous.

24. A method as recited in claim 23 wherein the noncancerous hyperproliferative disorder is psoriasis or benign prostatic hyperplasia.

25. A pharmaceutical composition for the treatment of hyperproliferative disorder in a mammal which comprises a hyperproliferative disease treating amount
10 of a compound of claim 1 and a pharmaceutically acceptable carrier.

INTERNATIONAL SEARCH REPORT

 Int. Application No
 PCT/IB 95/00061

A. CLASSIFICATION OF SUBJECT MATTER

 IPC 6 C07D403/04 C07D401/04 C07D413/14 C07D487/04 C07D491/04
 C07D403/14 C07F7/08 A61K31/505 A61K31/695
 //(C07D487/04, 209:00, 209:00), (C07D491/04, 319:00, 239:00),

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D C07F A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, vol. 71, May 1949 page 1893 GOODALE G.M. & MC KEE R.L. 'Quinazoline derivatives' see column 1 ---	1
X	US,A,4 012 513 (BIRCHALL G.R. ET AL.) 15 March 1977 cited in the application see scheme in columns 5/6; intermediates of formula (IX)	1,2,17
X	intermediates of formula (XIV) see column 5, line 45 - line 59 see column 39, line 3 - line 5 --- -/--	1,2

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- * & * document member of the same patent family

Date of the actual completion of the international search

13 April 1995

Date of mailing of the international search report

09.05.95

Name and mailing address of the ISA

 European Patent Office, P.B. 5818 Patentlaan 2
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Authorized officer

Hartrampf, G

INTERNATIONAL SEARCH REPORT

Int. Application No
PCT/IB 95/00061

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO,A,92 20642 (RHONE-POULENC RORER INTERNATIONAL) 26 November 1992 cited in the application see the whole document ---	1-25
Y	EP,A,0 520 722 (IMPERIAL CHEMICAL INDUSTRIES PLC) 30 December 1992 cited in the application see the whole document ---	1-25
Y	EP,A,0 566 226 (ZENECA LIMITED) 20 October 1993 cited in the application see the whole document ---	1-25
P,Y	EP,A,0 602 851 (ZENECA LIMITED) 22 June 1994 cited in the application see the whole document ---	1-25
P,Y	EP,A,0 635 498 (ZENECA LIMITED) 25 January 1995 see the whole document -----	1-25

INTERNATIONAL SEARCH REPORT

national application No.

PCT/IB 95/00061

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
ALTHOUGH CLAIMS 20 TO 24 ARE DIRECTED TO A METHOD OF TREATMENT OF
(DIAGNOSTIC METHOD PRACTISED ON) THE HUMAN/ANIMAL BODY, THE SEARCH HAS
BEEN CARRIED OUT AND BASED ON THE ALLEGED EFFECTS OF THE COMPOUND/COMPOSITION.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such
an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Inter-
national Application No
PCT/IB 95/00061

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A-4012513	15-03-77	GB-A- 1356834	19-06-74
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		BE-A- 790679	27-04-73
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		CH-A- 577499	15-07-76
		DE-A- 2253927	10-05-73
		FR-A,B 2158464	15-06-73
		JP-A- 48056667	09-08-73
		NL-A- 7214807	07-05-73
		SE-B- 384856	24-05-76
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		AT-B- 328431	25-03-76
		AT-B- 328432	25-03-76
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		EP-A- 0584222	02-03-94
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		AU-A- 1842292	07-01-93
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		NZ-A- 243082	24-02-95
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EP-A-0602851	22-06-94	AU-B- 5072893	23-06-94
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		CZ-A- 9302651	15-06-94
		FI-A- 935431	11-06-94
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		NO-A- 934504	13-06-94
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EP-A-0635498	25-01-95	AU-B- 7191694	20-02-95

Internal Application No
PCT/IB 95/00061

Form PCT/ISA/210 (patent family annex) (July 1992)